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THE NATURAL HISTORY OF CORONARY ARTERY DISEASE OF LONG DURATION

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CORONARY artery sclerosis is a particular manifestation of general arteriosclerosis and gives rise to symptoms only as it impairs the blood supply of the heart muscle. Angina pectoris, coronary thrombosis, and coronary insufficiency are not distinct clinical entities but are episodes in the slow, prolonged evolution of atheromatosis of the coronary arteries. Management of the patient with coronary atherosclerosis predicates familiarity with the natural history of the disorder which runs its course over many years or decades. In an attempt to obtain a comprehensive panorama of the clinical features of coronary artery disease, the records of 124 patients with this disorder were studied, each of whom has been under the author's personal observation for at least 10 years from the onset of the symptoms of heart disease. They represent patients who passed consecutively through the office, the only criterion of selection being the fact that they had been treated for 10 years or more. The fatal cases include all those in the "dead file" who had been treated for 10 or more years. It is impossible to determine how long the coronary disease had been latent in these patients before giving rise to evidences of cardiac impairment.

There were 115 men and 9 women (Table I). The average age at death or at the completion of the study was 61.9 years; the average duration of the symptoms of coronary disease was 13.6 years. The age at onset of the symptoms had no apparent effect on the duration of life nor on the course of the disease. The onset occurred in the fouth decade in 9, in the fifth in 63, in the sixth in 46, and in the seventh in 6. These figures have no significance in regard to the general prevalence of coronary artery disease, only in respect to persons who survive at least 10 years.

Figs. 1 and 2 give an over-all graphic survey of 31 living and 32 deceased patients. The black squares indicate episodes of myocardial infarction. The diagonal lines sloping down from right to left represent angina pectoris, and the superimposed numerals show the number of blocks the patient could walk before developing anginal pain. Diagonal lines sloping from left to right depict periods

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TABLE I. PATIENTS WITH CORONARY ARTERY DISEASE UNDER OBSERVATION FOR 10 OR MORE YEARS

	30 TO 39 YEARS			40 TO 49 YEARS			50 TO 59 YEARS			OVER 60 YEARS		
	DEAD	LIVING	TOTAL	DEAD	LIVING	TOTAL	DEAD	LIVING	TOTAL	DEAD	LIVING	TOTAL
Males												
No. of cases	6	2	8	24	36	60	17	25	42	3	2	5
Average age at onset	37.3	37.5	37.3	45.1	44.9	45.0	53.5	52.4	52.8	67.3	63.5	65.8
Average age at end of study	49.4	52.5	50.1	59.1	59.1	59.1	66.8	65.6	66.0	79.6	73.3	77.0
Average duration in years	12.1	15.0	12.8	14.0	14.2	14.1	13.3	13.2	13.2	12.3	10.0	11.2
Females												
Number of cases			1			3			4			1
Average age at onset			38.0			46.3			53.0			61
Average age at end of study			59.0			57.9			67.2			73
Average duration in years			21.0			11.6			14.2			12

of heart failure. Blank spaces denote the absence of symptoms. The striking fact that emerges from a superficial inspection of the charts is the great variability of the symptoms during the years of observation. In some patients the illness commenced with a myocardial infarction which was followed by symptoms of angina pectoris; in others there were no further symptoms for years following the infarction. Other patients began with the anginal syndrome and experienced myocardial infarctions at some subsequent time; still others never experienced a myocardial infarction. The intensity of the anginal symptoms varied from year to year, and commonly there were long periods during which the patient was free from cardiac complaints.

Twenty-six patients experienced no myocardial infarcts, 59 had 1 infarct, 24 had 2, 13 had 3, and 2 had 4. In 19 instances an infarct developed without giving rise to recognizable signs or symptoms and was discovered by routine electrocardiography. Such "silent" infarcts are quite common and are readily overlooked. The only indication of their development may be an anginal seizure of greater intensity than usual or, indeed, any change in the pattern of the anginal attacks. Any such alteration in the symptomatology of a patient with coronary artery sclerosis calls for the presumptive diagnosis of myocardial infarction until it is disproved by the subsequent course of events.

In 54 patients the symptomatology was ushered in by a myocardial infarction. Two of these experienced no further symptoms referable to the heart until they died 12 and 14 years later, respectively, from a second infarct. Six living patients have had no further symptoms after recovery from the original infarct.

In 69 patients the anginal syndrome first called attention to disease of the coronary arteries, and in 1 asymptomatic patient a routine electrocardiogram, taken for life insurance purposes, first disclosed myocardial damage. It appears that these long-term patients with coronary artery disease whose symptoms commence with simple angina pectoris have a better prognosis and a longer life than those in whom a myocardial infarction with recovery initiates the illness. The average duration of life, after the onset of symptoms, of those patients whose illness began with angina pectoris was 14.1 years with a mean deviation of 2.9 and an error of the mean of 0.236; of those with an initial myocardial infarction it was 12.7 years with a mean deviation of 3.1 and an error of the mean of 0.282. The difference between the means of the 2 series is 1.4 years, and its probable error is 0.367. Thus, the difference is 3.8 times the probable error. The average ages of the 2 groups were the same. Further confirmation of this trend is found in the patients who survived 15 years or more. Of these, 31 cases commenced with the anginal syndrome and only 7 with myocardial infarction. Yet in the whole series only 56 per cent of the cases began with angina pectoris.

No matter what the mode of onset, the course of the coronary disease was marked by fluctuations in degree of anginal pain, with episodes of coronary insufficiency or recurrent myocardial infarction, as well as by periods of well being. Some patients had persistent anginal pain of unchanged intensity during the entire period of observation; others gradually lost all symptoms after a number of years.

Fully 81 of the patients had no cardiac symptoms for 1 or more years. The variability of the periods of freedom from symptoms and the frequent occurrence

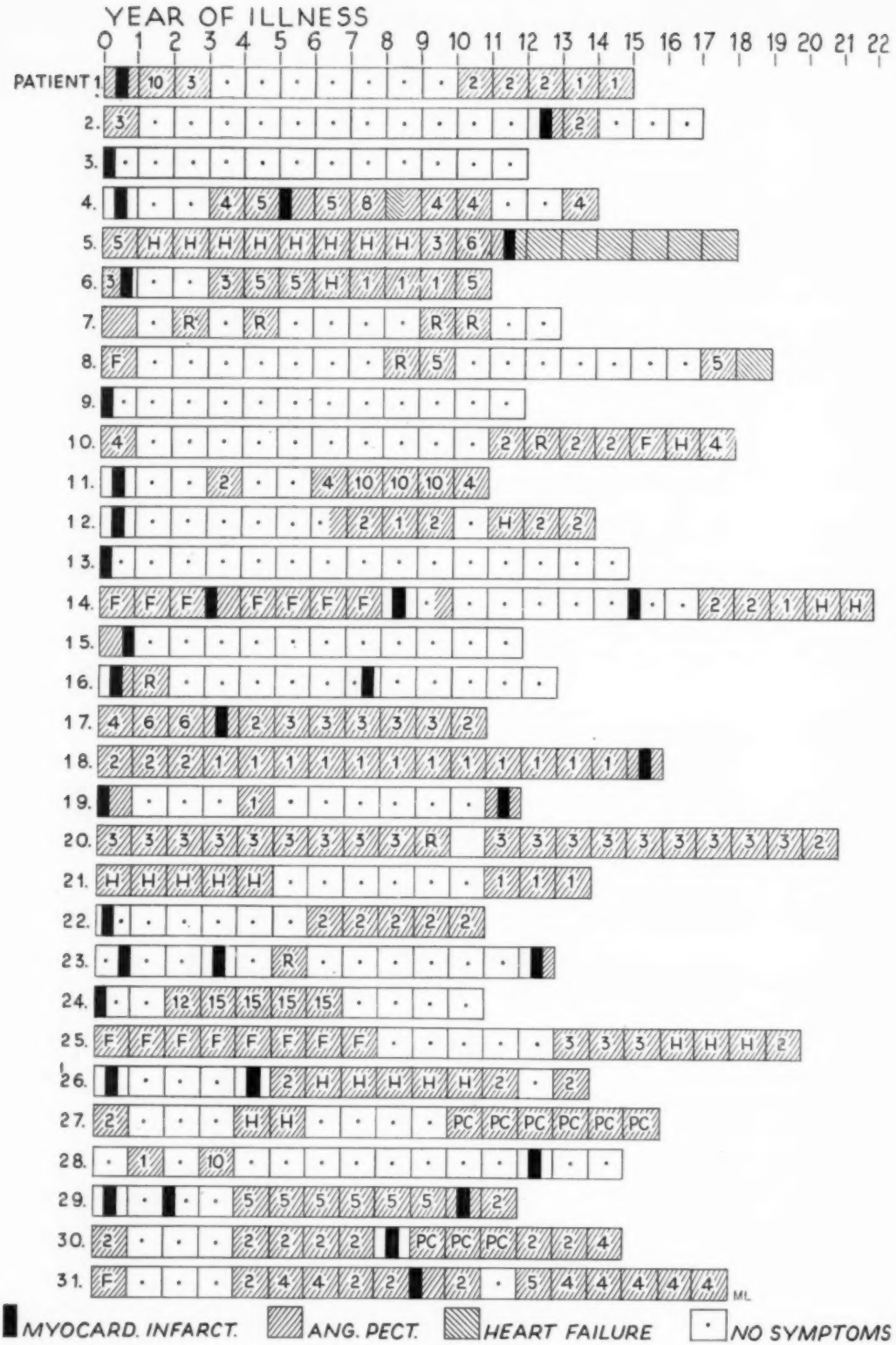


Fig. 1.—Thirty-one living patients. The numerals in the crosshatched squares indicate the number of blocks the patient could walk before experiencing anginal pain. *H*=angina on hills; *R*=angina at rest; *F*=angina on walking fast; *PC*=angina after meals; *E*=angina on excitement.

Fig. 2.—Thirty-two patients who died. The numerals in the crosshatched squares indicate the number of blocks the patient could walk before experiencing anginal pain. *H*=angina on hills; *R*=angina at rest; *F*=angina on walking fast; *PC*=angina after meals; *E*=angina on excitement.

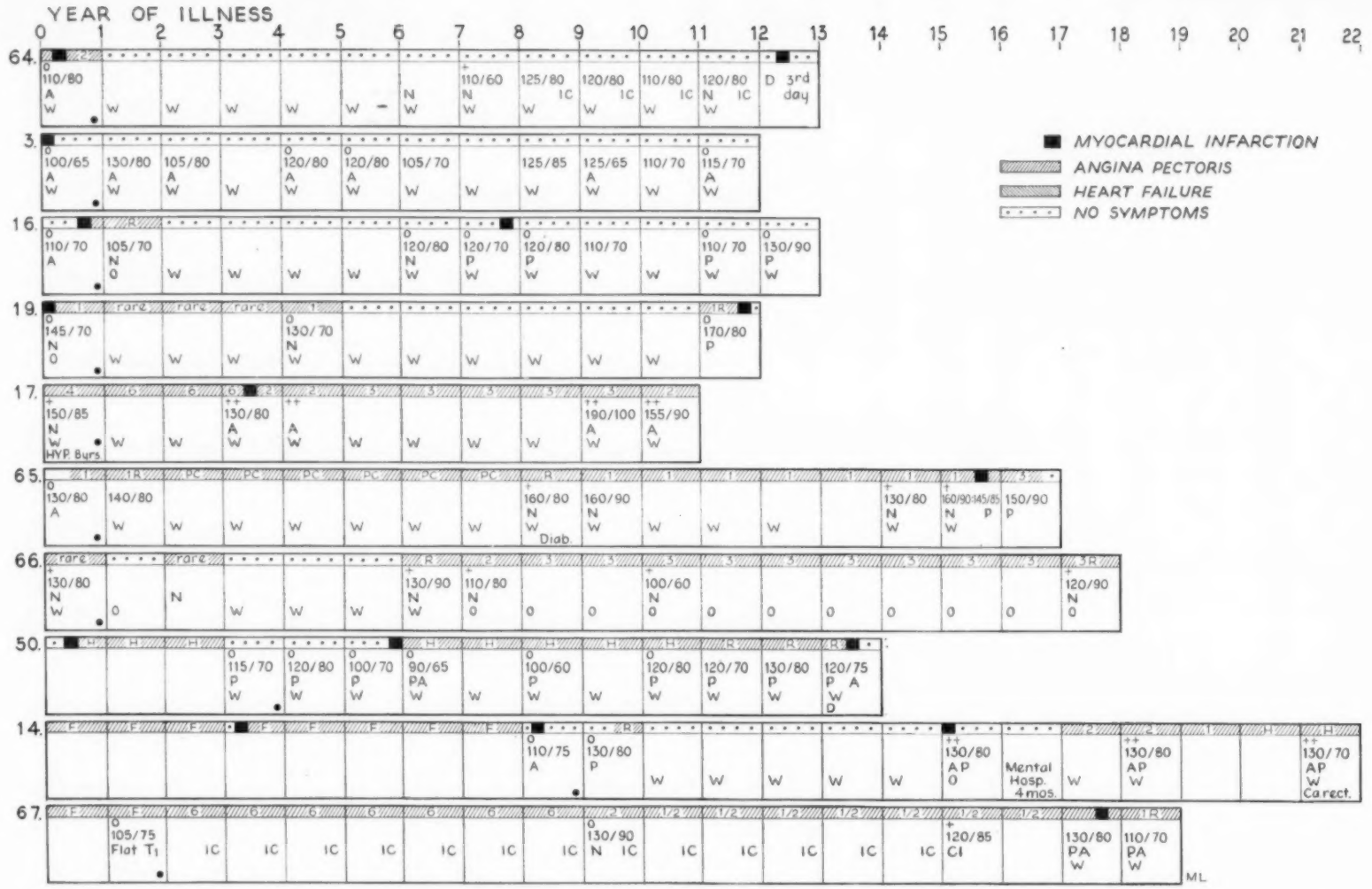
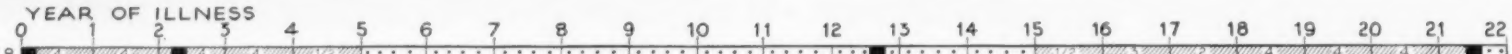


Fig. 3.—Detailed records of the course of coronary disease in selected cases. The symbols in the top line are the same as in Figs. 1 and 2. The second line indicates heart size: *O* = normal; +, ++, +++ = degrees of enlargement. The third line records blood pressure. The fourth line describes the electrocardiogram: *N*=normal; *A*=anterior wall pattern; *P*=posterior wall pattern; *AF*=auricular fibrillation; *CI*=coronary insufficiency pattern; *IC* (entered on fourth line to right)=intermittent claudication. The fifth line indicates: *W*=worked; *O*=did not work. The black dot indicates the year when the patient was first seen.



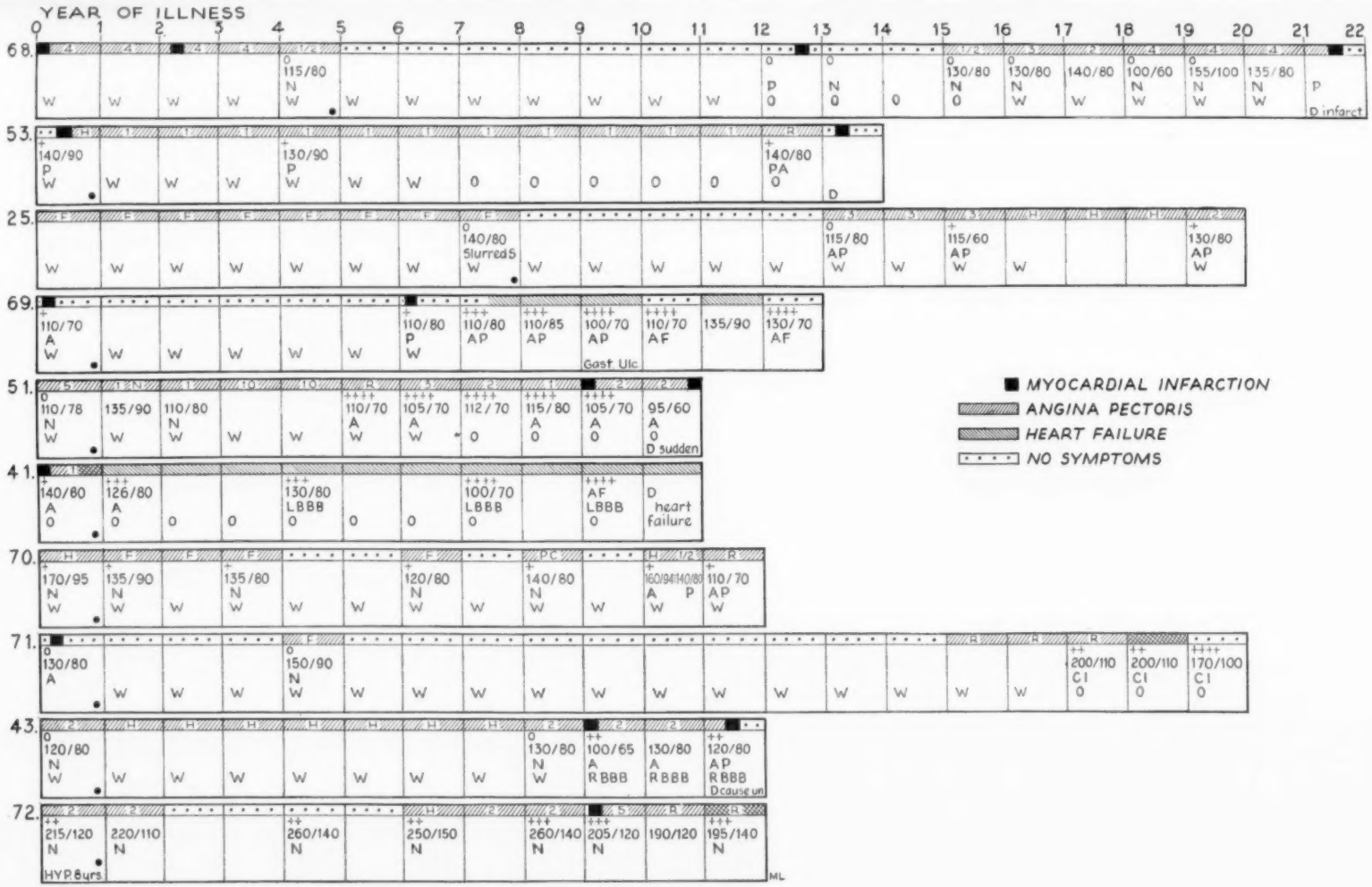


Fig. 4.—Detailed records of the course of coronary disease in selected cases. The symbols in the top line are the same as in Figs. 1 and 2. The second line indicates heart size: *0*=normal; +, ++, +++ = degrees of enlargement. The third line records blood pressure. The fourth line describes the electrocardiogram: *N*=normal; *A*=anterior wall pattern; *P*=posterior wall pattern; *AF*=auricular fibrillation; *CI*=coronary insufficiency pattern; *IC* (entered on fourth line to right)= intermittent claudication. The fifth line indicates: *W*=worked; *O*=did not work. The black dot indicates the year when the patient was first seen.

of many years of apparent health are well illustrated in the charts. Eighty-nine of the patients continued to follow their usual occupations during most of the period of observation. Fifteen did not work again after the onset of symptoms.

In 10 patients the electrocardiogram, which had had the typical configuration associated with myocardial infarction, returned to normal. This compares well with the experience of Mill and his associates[1] who found that in 9 of 100 patients who survived 1 to 6 years after myocardial infarction, the electrocardiogram showed a complete restitution to normal.

Thirty-four of the men and all of the 9 women had hypertension. This is a rather low incidence. It cannot be attributed to a persistent lowering of the blood pressure following myocardial infarction, for in most of the patients the level of blood pressure fluctuated within normal limits throughout the course of the illness and was not permanently deflected by a myocardial infarction. It may be that the selection of patients who survived 10 years or more eliminated many who had hypertension. In some patients the blood pressure was normal at the onset and gradually rose during the subsequent years. In still others a marked hypertension antedated the symptoms of coronary disease and persisted unabated during the years of observation.

Eight patients had diabetes, but in only 1 of them was glycosuria present at the onset of symptoms. In the others it developed some years after the appearance of symptoms of coronary artery disease.

Sixteen patients had intermittent claudication. In 3 instances peripheral arterial disease was present at the onset of the cardiac symptoms. In the other patients it developed after a variable number of years, from 1 to 15. It has recently been suggested that a reflex hypertension resulting from exercise of an ischemic leg may be the cause of cardiac hypertrophy in patients with intermittent claudication.[2] Four of these patients had cardiac enlargement that could not be explained by coexisting hypertension or severe myocardial infarction with heart failure.

Cardiac enlargement as determined by fluoroscopy was present in 20 patients in the absence of hypertension. In 5 of these patients the initial examination took place shortly after a myocardial infarction and revealed a large heart already. Although the blood pressure was normal and remained normal through the following years, it is barely possible that these patients had had an antecedent hypertension and that this had been responsible for the cardiac enlargement. In 15 patients, however, prolonged observation ruled out the presence of hypertension at any time in the course of their illness, but enlargement of the heart developed nevertheless. In only 2 patients was this accompanied by an aneurysm of the left ventricle. In 10 patients the enlargement of the heart seemed to follow directly on myocardial infarction, but in 5 the large heart bore no relationship to a recognizable infarct. Our data support the observation of others[3-4] that cardiac dilatation and hypertrophy may develop in patients with coronary artery sclerosis in the absence of hypertension or valvular disease. It is probably a compensatory reaction explained by Starling's law of the heart.[5] Such cardiac enlargement may develop without manifestations of gross heart failure. If it is true that intermittent claudication can lead to cardiac hypertrophy, this could have played a possible role in only 3 of the patients. None of the others had evidence of peripheral vascular disease.

Seventeen patients suffered from heart failure at some time during the course of their heart disease. In 7 the failure was directly precipitated by a myocardial infarction. Three of these had hypertension, 4 did not. In 6 patients heart failure apparently resulted from the effects of a long-standing hypertension and developed many years after a myocardial infarction. In 4 patients myocardial insufficiency could not be attributed to hypertension or to the immediate effect of an infarction but rather to enfeeblement of the heart muscle following some time after multiple myocardial infarctions. In all instances of cardiac failure the heart was enlarged. In some patients the appearance of heart failure led to death within a few months, but several lived for many years after myocardial insufficiency first developed—1 as long as 9 years. The low incidence of heart failure in this series may be accounted for by the fact that most patients with coronary artery disease who develop heart failure die soon thereafter, so that few would be in a group who survived 10 years or more.

The causes of death of the 53 patients who died were as follows:

Myocardial infarction	21
Sudden death	11
Heart failure	3
Cerebral vascular insult	3
Noncardiac disease	6
Unknown	9
	53

SUMMARY

The clinical course of 124 patients who had been under observation for coronary artery disease for at least 10 years is described and graphically portrayed. The average duration of cardiac symptoms was 13.6 years. Patients whose illness began with simple angina pectoris had a better prognosis than those in whom it was initiated by a myocardial infarct.

Fifteen patients who never had hypertension developed cardiac enlargement.

Sixty-five per cent of the patients were without symptoms for 1 or more years, and 72 per cent followed their usual occupations during most of their illness.

The study emphasizes the unpredictable, variegated course of coronary artery disease and the frequent modifications of symptomatology in patients with this disorder.

Miss Mary Lorenc of New York University College of Medicine, New York, N. Y., drew the charts.

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ACUTE MYOCARDIAL INFARCTION WITH RUPTURE OF THE VENTRICLE

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ALTHOUGH rupture of the heart has been known as a clinical entity for 3 centuries, it has come into prominence only with a better understanding of myocardial infarction. Harvey is said to have described the entity in 1647.[1] In 1765, Morgagni reported 11 cases of rupture of the heart,[1] and he placed the cause of rupture on marked fatty myocardial changes. It is interesting that Morgagni himself died of a ruptured heart.[2] Marie, in 1896, was the first to connect correctly coronary artery disease with myocardial infarction.

This clinical entity is not at all rare. Krumbhaar and Crowell reviewed the literature in 1925 and found a total of 654 cases.[3] They added 22 cases of their own. An incidence of 9.5 per cent was reported in a series of 105 cases of acute myocardial infarction by Friedman and White.[4] These authors also cited the statistics of Mortlan, who found 42 cases of ruptured heart in a series of 2,000 instances of sudden death. Turnbull and Howell reported 8 cases over a 6 year period.[5] Diaz-Rivera and Miller presented a series of 5 ruptured hearts out of a total of 147 cases of myocardial infarction.[6] All five cases occurred in a group of 53 recent infarctions. In 94 old infarctions of that same series, there were no instances of rupture of the heart. The consensus of the literature places the incidence at approximately 9 per cent in acute myocardial infarction. Jetter and White reported a higher incidence in patients in a mental institution.[7] In their 22 cases there were 16 instances of rupture, an incidence of 73 per cent. The authors stated that in no case was an antemortem diagnosis of myocardial infarction made.

We have observed 6 cases of rupture of the ventricle following acute myocardial infarction at The Toledo Hospital. It is the purpose of this paper to present and discuss these cases from the etiologic, pathologic, and diagnostic viewpoints, including a review of the recent literature.

CASE REPORTS

CASE 1.—A 71-year-old man was admitted to the hospital with a 3 hour history of severe substernal pain radiating down both arms, constriction in the chest, and shortness of breath. He had been having anginal attacks for a few months. His admission blood pressure was 180/100 mm. Hg, and it did not change until immediately preceding death. Except for an apical systolic murmur, physical examination of the heart was negative. The electrocardiogram showed an extensive acute anterior myocardial infarction. Treatment included anticoagulants and sedation.

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Progress was apparently good until the second hospital day. At that time the patient's heart tones became distant and the pain increased. There was no friction rub. Two hours later the patient died.

Post-mortem study revealed a hemopericardium. The heart weighed 400 grams. All the chambers of the heart were moderately distended. The left coronary artery was occluded by a firm red clot. There was infarction of almost all of the anterior wall of the left ventricle. Extensive necrosis with undermining and dissection of the myocardium and marked polymorphonuclear leucocytic infiltration was noted. In the middle of this area, midway between the apex and base of the heart, there was a ragged laceration filled with post-mortem clotted blood.

The factors responsible for rupture were the sustained hypertension, extensive undermining of the necrotic myocardium, and hemorrhage into the necrotic tissue.

CASE 2.—A 73-year-old white woman was admitted to the hospital with sore throat, cough, weakness, and dull pain in the left chest. She had been admitted in 1938 for a cholecystectomy because of cholelithiasis and multiple abscesses of the gall bladder wall; in 1942 for hepatitis, duodenitis, and choledochitis; and for investigation of chronic fatigue and anemia in January, 1947, at which time the electrocardiogram was interpreted as showing an impaired myocardium. On her final admission, 3 months later, she was in moderate heart failure. Auscultatory findings in the heart were consistent with aortic and mitral stenosis and mitral insufficiency. The electrocardiogram showed atypical right bundle branch block and evidence of myocardial damage in the anterior wall and interventricular septum. Because of progressing congestive failure, she was treated with digitalis. Her clinical course was that of unremitting congestive failure and uremia. She died on the twelfth hospital day.

Post-mortem study showed hemopericardium and patchy acute pericarditis. The heart weighed 425 grams. Subepicardial fat was increased in amount. The left anterior descending branch of the left coronary artery was completely occluded. There was an acute infarction of the lower half of the anterior wall of the left ventricle. An aneurysmal dilatation of this heart chamber was noted. In the center of the infarcted area, surrounded by extensive myocardial fragmentation and necrosis and invaded by polymorphonuclear leucocytes, was a ragged laceration. Study of the valves revealed aortic and mitral stenosis.

Factors contributing to rupture in this patient were the extensive character of the infarct and high intracardiac pressure due to aortic valvular disease, possibly increased by medication.

CASE 3.—A 68-year-old white man was admitted to the hospital with nonradiating, severe substernal pain of 1 day's duration. He had had a similar attack 1 month previously. Physical examination on admission revealed a diastolic hypertension with a blood pressure of 132/102 mm. Hg. The heart tones were of poor quality, and a transient friction rub was heard. The electrocardiogram showed an acute posterior myocardial infarction. Routine therapy was instituted. On the second hospital day, the patient's brother came to visit. He was intoxicated and created a disturbance. A few minutes later the patient suddenly died.

Post-mortem study revealed hemopericardium with scattered areas of pericarditis. The right coronary artery was completely occluded. There was partial occlusion of the left coronary artery. The area of infarction, 3 cm. by 5 cm., located just below the posterior leaflet of the mitral valve, showed progressive dissection of the necrotic myocardium for a distance of 2 cm., leading into a 1 cm. defect in the epicardium in the center of the infarcted area. Polymorphonuclear leucocytes were noted in increased numbers.

Without doubt, the emotional upset was the precipitating factor in rupture of the heart. Other conditions contributing to rupture were a persistently elevated diastolic blood pressure and the transmural character of the infarct, as indicated by very deep Q waves in Leads II and III of the electrocardiogram. There was insufficient time for the anticoagulant medication to be a factor in this case.

CASE 4.—A 74-year-old white woman had a 2 month history of substernal distress and tightness, with radiation of the pain into the neck, down the left arm, and into the interscapular area. Over this 2 month period the attacks had become more severe, more frequent, and were brought on by less exertion. The attack on the day of admission to the hospital was the most severe that she had ever experienced and was associated with dyspnea and restlessness. The heart tones were of poor quality. The blood pressure was 140/80 mm. Hg. There were no other

abnormal physical findings. The electrocardiogram showed an acute anterior myocardial infarction. Routine therapy with oxygen, anticoagulants, vasodilators, and morphine was administered. It was never possible to relieve the patient's pain completely. She remained quite restless, rolling constantly from side to side. She died suddenly on the third hospital day.

At post-mortem examination hemopericardium was found. The heart weighed 380 grams. Subepicardial fat was increased in amount. The left coronary artery was completely occluded. A large infarction, 6 cm. in diameter, was found on the anterior wall of the left ventricle. In the middle of this area, 4 cm. from the apex, was a "blow-out" type of defect in the myocardium. Surrounding this defect were extensive necrosis and fragmentation of the myocardium with infiltration by polymorphonuclear leucocytes. Multiple gray, nodular thickenings were seen on the mitral valve leaflets.

In this patient rupture was due to a relative hypertension associated with a small heart. Although anticoagulant therapy was well under way, no increased hemorrhage into the site of rupture was seen.

CASE 5.—A 73-year-old white woman was admitted to the hospital with the history of having been awakened from sleep by severe diarrhea. Seven hours later, she became nauseated and vomited. There also developed a dull chest pain with radiation down the left arm and to the left side of the back. She had had many previous illnesses, including "several kidney operations," a slight cerebral vascular accident, several fractured vertebrae, a broken shoulder, a urethral caruncle, and "arthritis for years." An attack of chest pain was first noted 4 months prior to admission.

The admission blood pressure was 174/120 mm. Hg, the heart was enlarged to percussion, and there was a soft apical systolic murmur. Bilateral basal r les were noted in the lungs. Routine therapy was instituted. The blood pressure remained elevated at 150/90 mm. Hg. On the seventh hospital day, frank congestive failure developed, the heart tones became poor in quality, and an electrocardiogram showed progressive extension of the infarction. On the ninth day, following a spasm of pain, she suddenly died.

Post-mortem examination revealed a hemopericardium. The left anterior descending branch of the left coronary artery was completely occluded. There was an aneurysmal dilatation of the left ventricle, and its anterior wall had a large infarcted area with a 5 cm. laceration located 3 cm. from the apex of the heart. Extensive myocardial necrosis, fragmentation, and undermining were noted. Polymorphonuclear infiltration was increased.

The important factors which contributed to the rupture in this patient were persistent hypertension, extension of the original infarct, marked anticoagulant activity as evidenced by a prothrombin time of 39.5 seconds on the day before death, and progressing congestive heart failure.

CASE 6.—A 76-year-old white woman was admitted to the hospital with a history of angina pectoris for 10 years. She had been awakened from sleep an hour and one-half before admission by pain of the same type, but more severe; profuse sweating and the urge to defecate were associated. She went to the bathroom and had a large bowel movement immediately after which the pain became more intense. Physical examination on admission revealed a short systolic murmur at the apex. The heart tones were of poor quality. The electrocardiogram showed an acute posterior myocardial infarction. She was a known diabetic, and her admission urine showed a 2 plus test for sugar.

During the first hospital day she became disoriented, climbed out of bed, and paced the floor constantly. She rejected all attempts at sedation. On the second day a dull pain was noted in the left shoulder, and she died shortly afterwards.

Post-mortem study showed hemopericardium, an aneurysmal dilatation of the left ventricle, and an extensive infarction of the posterior wall of the left ventricle. There was marked necrosis, undermining, and dissection of the myocardium. In this same area, midway between apex and base of the heart, there was a ragged laceration that communicated with the cavity of the left ventricle.

The cause for rupture in this patient was physical activity during the acute phase of the infarction. In addition, there was progressing perforation without the patient's complaining of pain

RESULTS

An analysis of the clinical data shows that the range of ages in these 6 patients was from 68 to 76 years, the average being 72 years. Four of the patients were women, whereas the majority of patients admitted to this hospital with acute myocardial infarctions are men.

A history of a previous infarction was given by 1 patient only, Case 3. This patient had had an episode of anginal pain 1 month before admission, but was not diagnosed as having had an acute infarction. Evidence of a previous infarction was lacking in the electrocardiogram. Angina pectoris or anginal-type pain was present in 5 patients. The duration of repeated attacks of this nature ranged from 1 month to 10 years. In all instances the type of pain during the terminal infarction was the same as that during the previous anginal attacks, except for increased severity. Three of the 4 women had a history of anginal attacks; both men had had previous attacks of angina.

Hypertension, persistent even after infarction, was noted in 4 patients. In 3 of these the diastolic pressure was 100 mm. Hg or over. All the patients with hypertension had a history of anginal-type pain previous to infarction.

Three patients had inadequate bed rest. In Case 3, rupture of the heart followed immediately after the patient was disturbed by an intoxicated brother. Another, Case 6, became irrational, got out of bed, and resisted all attempts at control. The third, Case 4, cooperated well, but was extremely restless.

Analysis of the symptoms showed that all of the patients had pain typical of acute infarction, differing in no way from pain accompanying infarcts that do not rupture. New soreness or pain developed in 2 patients. Radiation of pain into the back occurred twice.

On physical examination, the heart tones were of poor quality in all cases. A transient pericardial friction rub was heard in 1 patient. Four patients had heart murmurs, all systolic in timing; 2 of these were associated with some type of valvular deformity (Cases 2 and 4). Irregularity of heart rhythm was noted in 2 instances. Congestive heart failure occurred twice, once associated with advanced renal damage and chronic hypertension (Case 2).

On post-mortem study it was seen that in each case the site of rupture was through an infarction, the involved area being in the anterior wall of the left ventricle in 4 patients and in the posterior wall in 2 patients. The site of rupture was approximately midway between apex and base in every case. Aneurysmal dilatation of the infarcted ventricle was seen 3 times. A fourth patient showed moderate dilatation of all heart chambers.

The types of rupture were divided into 2 classes, the "blow-out" and the "dissection" types. The "blow-out" type, in which the laceration was sharp and clean, was seen only in Case 4. Found in the remaining 5 cases was the "dissection" type in which the laceration was ragged and associated with necrosis, undermining, and dissection of the myocardium for as long a distance as 2 cm., as in Case 3. Polymorphonuclear leucocytic activity was increased in 3 instances.

In 4 of the patients, rupture of the infarcted ventricle occurred within the first 3 days. The other 2 ruptures occurred on the ninth and twelfth days. The average time of rupture was on the fifth day.

The most important factors contributing to production of rupture were the location of the infarct, the extent of infarction, the amount of undermining and dissection of the necrotic myocardium, and the persistence of hypertension after the initial shock of infarction.

DISCUSSION

Pathology and Mechanism of Rupture.—Knowledge of the pathology of myocardial infarction is essential to the understanding of the factors predisposing to and precipitating rupture. Mallory, White, and Salcedo-Salgar presented an excellent discussion of the pathological findings during the healing of myocardial infarction.[8] They found that during the first 4 days there were no signs of healing, only signs of muscle necrosis and degeneration, marked polymorphonuclear infiltration, and necrosis of many of the polymorphonuclears. It is known that necrotic polymorphonuclears liberate a proteolytic enzyme that increases softening and liquefaction of the necrotic myocardium[1]; combination of these factors in large infarcts leads to extensive myocardial necrosis with undermining and dissection of the myocardium with formation of sinuslike tracts.[6] Much hemorrhagic extravasation into these areas is also seen. This predisposes toward rupture. Snyder described similar findings.[9]

In the light of these facts, it is important to note that the myocardium is at its weakest during the first 4 days and is most likely to rupture during that time. Indeed, 4 of our patients ruptured within the first 3 days. Meakins stated that it is seldom that a patient comes to autopsy with rupture that has not occurred within the first 4 days after the infarction.[10] That 2 of our patients ruptured at 9 and 12 days, respectively, is support for the general consensus that rupture may occur within a 2 or 3 week period after infarction.

Also important in production of rupture is the location of the involved infarct. From a review of 738 cases gathered from the literature, including our cases (Table I), it is noted that the most frequent sites of rupture were in the left ventricle, 80.9 per cent, and in the right ventricle, 9.2 per cent. Rupture through other areas was comparatively rare. Anterior perforation occurred in 75 per cent and posterior perforation in 25 per cent of the 80 patients in whom the position of the rupture was described. This increased incidence of anterior perforations parallels the increased frequency of myocardial infarctions anteriorly.

In all our patients, the site of rupture was approximately midway between the apex and base of the heart. In the cases presented by Segall[11] all ruptures were within 5 or 6 cm. of the apex. Review of the cases of Krumbhaar and Crowell[3] shows that of the 16 instances in which the site of rupture was described, the nearest to the apex was 2.5 cm. distant. In the same series, the greater majority of the ruptures were approximately midway between apex and base. This area, anatomically, is the thickest portion of the heart and is under greater stress during systole than other portions of the heart. If, in addition to infarction, this area is further weakened by extensive undermining and dissection and subjected to strain, predisposition to rupture is increased. That the "dissection" type of rupture was seen in 5 of our 6 patients is strong evidence favoring this theory. Further support for this view is found in the work of Krumbhaar

and Crowell.[3] In describing the ventricular lacerations in 166 patients, they found an irregular, jagged defect in 43.5 per cent. Another 14.4 per cent had marked infiltration of the defect with blood. The defect was clean cut in only 12 per cent.

TABLE I. LOCATION OF MYOCARDIAL INFARCTIONS ASSOCIATED WITH RUPTURE

	NUMBER OF CASES	LEFT VENTRICLE	LEFT VENTRICLE ANTERIOR	LEFT VENTRICLE POSTERIOR	RIGHT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE, LEFT VENTRICLE, INTERVENTRICULAR SEPTUM COMBINATION
Krumbhaar and Crowell[3]	292	225			32		20	8	
Edmondson and Hoxie[1]	69	52	37	10	4	13			
Quain and associates*	318	268			31		15	4	
Jetter and White[7]	16	15							1
Friedman and White[4]	10	10	8	2					
Turnbull and Howell[5]	8	7	3	4					1
Gans	6	6	4	2					
Diaz-Rivera and Miller[6]	5	4	3	1		1			
Segall[11]	4	3	2	1					1
Simburg[26]	2	2	2						
Carroll and Cummins[27]	1	1							1
Bayley and Fader[25]	1					1			
Bickerman and Irons[24]	1					1			
Sevitt[22]†	1				1				
Selby[12]	1	1							
Snyder[9]	1	1	1						1
Fisher[29]	1	1	1						
Moolten[23]	1					1			
Total	738	596	61	20	68	17	35	12	5

*Cited by Krumbhaar and Crowell.[3]
†No actual infarction was described in this case.

Once the above-described factors predisposing to rupture are present, a variety of other factors may precipitate actual rupture. Elevated intracardiac pressure is a common precipitating factor. Persistent hypertension was noted in 4 of our patients. Edmondson and Hoxie found that hypertension was twice as common in patients with fatal, ruptured infarctions as in fatal, non-ruptured infarctions.[1] Physical exertion, be it due to too early ambulation or inadequate bed rest, and coincident congestive heart failure with or without valvular disease, both increase the load on the injured heart and, therefore, may precipitate rupture. Digitalis therapy, indicated as a life-saving measure in progressing congestive failure associated with acute infarction, may also precipitate rupture.[12]

It has been suggested that anticoagulant therapy may increase the incidence of rupture. Blumgart and associates,[13] in their studies on experimental coronary occlusion in dogs, found that there was no increase in the incidence and magnitude of hemorrhagic extravasations in infarcted hearts of dogs given Dicumarol.

Krumbhaar and Crowell[3] listed the exciting cause of rupture in 43 patients: 14 died while eating, 13 while walking, 10 during defecation, and 6 while getting out of bed.

Symptoms, Diagnosis, and Prognosis.—The symptomatology of an acute myocardial infarction that ruptures does not differ in any way from that of an infarction that does not rupture. However, the development of new pain, especially if it is severe and boring in character, is suggestive of extension of the infarction and possible impending perforation. Since rupture may occur within the first 2 or 3 weeks, any significant change from the normal trend of a healing infarction, especially during the first few days, should be viewed with alarm. Persistent hypertension, especially diastolic hypertension, causes apprehension of a possible rupture. In most cases, the heart tones will be of poor quality. The significance of systolic murmurs is questionable.

The development of an aneurysmal dilatation is common and causes suspicion of impending perforation. True aneurysm does not usually occur early in the course of an acute infarction, although it has been described as early as 3 months.[14] Excellent criteria have been described for the antemortem diagnosis of this entity.[15-21] The use of the roentgenogram, fluoroscopy, roentgenkymography,[22] and the electrocardiogram[16,17] aid in confirming the diagnosis.

A special type of rupture following acute infarction is one through the interventricular septum.[23,24,25] Here, the patient does not die immediately of cardiac tamponade, as in other types of rupture. Rather, he dies of unremitting failure of the right side of the heart some variable time after rupture.

Once the ventricle has ruptured, whether into the pericardial cavity or through the interventricular septum, the patient's fate is sealed. The best treatment, therefore, lies in prophylaxis, in adequate treatment of the acute infarction.

SUMMARY AND CONCLUSIONS

1. The history of rupture of the ventricular myocardium following acute myocardial infarction has been reviewed briefly.

2. The incidence of rupture following acute myocardial infarction is approximately 9 per cent. It occurs most frequently between the ages of 65 and 75 years.

3. Rupture of the ventricle most frequently occurs within the first 4 days. However, the general consensus is that it may occur during the first 2 to 3 weeks following acute infarction.

4. The most important features found at post-mortem examination were as follows:

   A. The involved infarct is most often located midway between the apex and the base of the heart, most often on the anterior surface of the left ventricle.
   B. There are extensive myocardial necrosis, undermining and dissection, and hemorrhagic extravasation at the site of rupture.
   C. The most common type of laceration encountered is the ragged "dissection" type.
   D. A less common type of laceration is the "blow-out" type.

5. The main factors in the mechanism of rupture are: (a) the location of the infarct; (b) the type of disease found at the site of rupture; (c) high intracardiac pressure due to persistent hypertension, especially diastolic hypertension, after the initial shock of infarction; (d) undue physical and emotional strain; and (e) progressive heart failure.

6. The best treatment for rupture of the heart lies in its prevention by adequate treatment of the acute infarction.

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CARDIAC ANEURYSM: CLINICAL AND ELECTROCARDIOGRAPHIC ANALYSIS

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DURING the past 15 years the diagnosis of ventricular aneurysm has been made ante mortem with increasing frequency. Primarily, this has been the result of expanding knowledge of the pathogenesis, clinical course, and roentgenologic manifestations of such aneurysms. Reports dealing with the clinical features[1-11] are in general agreement. However, there is no agreement concerning the value of the electrocardiogram as an aid in diagnosis. The purpose of this communication is to review the clinical and roentgenologic manifestations and to present further electrocardiographic data based on the concepts of Wilson and associates[12, 13] and their development by others.

The clinical material for this communication consists of 20 cases of ventricular aneurysm. Twelve of these have been substantiated by necropsy and the remaining 8 by suitable clinical and roentgenologic studies. Three of the antemortem group are considered "idiopathic" aneurysms, since no definite etiologic basis exists. The entire group includes 16 male and 4 female patients. The average age at the time of diagnosis was 62 years with a range of 42 to 86 years. Fourteen of the patients were observed for at least 1 month, the longest period of observation being 5 years.

PATHOGENESIS

At least 85 per cent of all ventricular aneurysms follow myocardial infarction,[3,9-11] particularly after large transmural infarcts with extensive destruction and fibrous replacement of the ventricular wall.[14] High intracardiac pressure during ventricular systole causes bulging of the weakened wall to produce the aneurysm. At this stage, the patient may succumb with congestive failure, arrhythmia, embolism, or rupture of the aneurysm, or healing of the area may occur with permanent aneurysm formation. Healing may occur with or without calcification in the wall of the aneurysm.

The incidence of ventricular aneurysm following myocardial infarction is generally reported to be 8 to 10 per cent of all cases.[3,15,17] Much higher figures have also been reported.[18] Aneurysm of slight degree is common following extensive myocardial infarction.[10] It has been demonstrated in dogs that adequate rest following experimental myocardial infarction insures a small, firm scar, while early exercise results in a thin, bulging aneurysmal scar.[19] Aneurysm formation in man is known to occur as early as 1 week following infarc-

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tion[10,11]; in some instances it occurs months or even years after infarction. Of the 20 cases reported here, only 3 were known to have had an adequate period of bed rest following infarction. Several developed the aneurysm following "silent" infarction. Eleven of the patients gave no history of chest pain or acute cardiac failure. Most of the aneurysms were discovered after the patient entered the hospital with congestive heart failure of insidious onset. These observations support the views of others[2,5,6,10] that early ambulation following myocardial infarction plays an important role in enhancing aneurysm formation.

Ventricular aneurysm may follow other pathologic processes which produce localized weakness in the myocardial wall: myocardial abscess from infected emboli, erosive or mycotic aneurysm arising from endocarditis, rheumatic necrosis of the myocardium, syphilitic gumma of the myocardium, and trauma; it may be congenital, which is mainly of the membranous septum, or idiopathic.[3,9,20]

It has been stated that normal or low blood pressure is characteristic of ventricular aneurysm.[3,11] This led to the postulate[3] that aneurysm would not develop in a myocardium hypertrophied by pre-existing hypertension. This point of view was not supported by Brams and Gropper[5] who found evidence of hypertension in one-half of their series of 21 patients. In the 20 cases reported here, hypertension was present in the majority. Diastolic pressures of 100 mm. Hg or more were recorded in 10 of the patients. An additional 3 patients had good evidence of pre-existing hypertension even though the diastolic pressures were normal at the time of observation (heart weight 735 grams without valvular disease; history of hypertension for 8 years with severe arteriolonephrosclerosis at necropsy; marked arteriosclerosis at the age of 79 years with blood pressures of 160/90 and 200/90 mm. Hg). Our observations indicate that a hypertrophied myocardium does not necessarily protect against aneurysm formation following extensive myocardial infarction. Indeed, hypertension with its associated increased cardiac effort should offer ideal conditions for the development of ventricular aneurysm following myocardial infarction.

PATHOLOGY

Most aneurysms are located at the cardiac apex, usually of the anterior or anterolateral aspect of the left ventricle, and may involve the anterior or lower portion of the interventricular septum. Many involve a greater portion of the anterior or anterolateral left ventricular wall. Apical and anterolateral aneurysms usually follow occlusion of the anterior descending branch of the left coronary artery.[3,9,10] Despite the frequency of posterior myocardial infarction, aneurysm of this portion of the ventricular wall is much less common.[11] Aneurysm of the interventricular septum alone or of the free wall of the right ventricle is rare.[10,11] In a review of a large number of ventricular aneurysms, both personally observed and from the literature, Schwedel[21] gives the frequency of location as follows: (1) 61 per cent at the apex of the left ventricle, anterior, lateral, or posterior aspect; (2) 19 per cent at the posterobasal portion of the left ventricle; and (3) 20 per cent high at the anterior or anterolateral portion of the left ventricle. In 10 per cent of the patients there was more than 1 aneurysmal bulge, the second site involving the interventricular septum or the right ventricle.

In the series reported here, 17 aneurysms involved the left ventricle, 1 involved the right ventricle, 1 was confined to the interventricular septum and was associated with a recent apical myocardial infarct, and 1, mycotic in origin, was confined to the interventricular septum and had ruptured into the right ventricle. Of the 17 left ventricular aneurysms, 6 were apical, 9 high anterolateral, and 2 posterobasal in location.

The myocardium is extensively thinned and replaced by fibrous tissue in the aneurysmal area. The usual form is a simple outward bulge at the site of a previous transmural infarct. The pericardium is adherent and frequently calcified; adhesions to adjacent visceral or parietal pleura are common. An underlying endocardial mural thrombus, which may be calcified, firmly fixed, or fragile and a source of systemic emboli, is common.[17] The size of the aneurysm depends upon the area of weakened myocardium; small aneurysms are common and often overlooked. Most isolated reports in the literature deal with large easily diagnosed aneurysms.

Rupture of a chronic ventricular aneurysm may occur,[15,22] but this is unusual. Wang, Bland, and White[16] reported that of 52 large ventricular aneurysms (38 anterior, 11 posterior, and 3 interventricular septum), there was rupture of the anterior wall in 21 cases and of the interventricular septum in 1 case, but none of the posterior wall. In 2 other large series[5,7] totaling 64 cases, rupture of an aneurysm was not found. The stage of organization following myocardial infarction is important, since cardiac rupture is rare after a firm scar forms.

CLINICAL FEATURES

There are *no symptoms* characteristic of ventricular aneurysm. Any symptoms present are nearly always those consequent upon extensive myocardial infarction. Many of the group reported here sustained "silent" myocardial infarctions and presented themselves with congestive heart failure of insidious onset. Ventricular aneurysm may be found in an individual completely free of cardiac symptoms. Ball[2] emphasized that congestive failure develops rather quickly in individuals who have aneurysm associated with coronary artery occlusion.

Physical signs are variable and usually unreliable. The only important sign is pulsation separate from that of the apex. When present, it is usually medial to and above the apical impulse.[5,6,9] Such a finding is neither constant nor pathognomonic.[21] A displaced, diffuse, and heaving apical impulse may be found in large hearts with or without aneurysm. There may be a percussible bulge at the left border of the heart if the aneurysm is situated high on the anterolateral portion of the left ventricle and if it approaches the chest wall. Most aneurysms, however, are located at the cardiac apex and cannot be distinguished from left ventricular enlargement by physical signs.

Ventricular aneurysms do not produce characteristic cardiac murmurs. Systolic murmurs are frequently mentioned but have no diagnostic characteristics. Diastolic murmurs are occasionally present and have been recently reviewed by Scherf and Brooks.[23] Those heard and recorded were loudest over the area of the aneurysm, high pitched, soft, and ended with presystolic accentua-

tion. This diastolic murmur must be differentiated from the third heart sound of gallop rhythm, pericardial rub, and the murmur of aortic regurgitation, with which it is most frequently confused. How the ventricular aneurysm produces a diastolic murmur is not known. In the series reported here, murmurs were absent in 13, systolic apical murmurs were present in 5, and a diastolic murmur was present in 1. In the last instance, the murmur was due to aortic insufficiency in a patient with active rheumatic aortic valvulitis and subacute bacterial endocarditis. At necropsy the patient was found to have a perforated mycotic aneurysm of the interventricular septum. One patient with a recent anteroseptal infarct and aneurysm of the interventricular septum exhibited a change from a loud, blowing, systolic precordial murmur to a systolic and diastolic murmur which extended throughout the length of the heart cycle on the day of death. Systolic apical murmurs in the 5 instances had no diagnostic characteristics.

Gallop rhythm has been described but is not limited to cardiac aneurysms. Similarly, a diminished or muffled heart sound with disproportion between the sound and the forcefulness of the pulsation is inconstantly present.[8]

ROENTGENOLOGIC MANIFESTATIONS

Ventricular aneurysms are being discovered ante mortem with increasing frequency, principally through the expanded use of chest roentgenograms and cardiac fluoroscopy. Since cardiac aneurysms vary in their location, adequate roentgenologic examination requires multiple plane projections of the chest and careful fluoroscopy, particularly if small aneurysms are to be demonstrated. Schwedel[21] gave the following radiographic criteria for the diagnosis of ventricular aneurysm: (1) localized bulge; (2) pericardial adhesions giving systolic traction on adjacent lung or diaphragmatic pleura, although all such adhesions are not due to ventricular aneurysm; (3) increased density due to mural thrombus which may occasionally contain calcium deposits; (4) ventricular incisura or angulation between the site of the bulge and uninvolved portions of the ventricle; and (5) abnormal pulsations. In the majority of instances, pulsation of a ventricular aneurysm is asynchronous or contrapulsile, bulging outward when the remainder of the ventricle contracts. However, and especially in the presence of a mural thrombus, pulsation may also be synchronous and systolic as well as strong or weak. When the left ventricle is enlarged, a segment which shows diminished amplitude of pulsation alone is not sufficient for a diagnosis of ventricular aneurysm. When such a segment of diminished amplitude is associated with pericardial adhesions, increased density, or a ventricular incisura, the diagnosis of ventricular aneurysm is enhanced. It is difficult or impossible to diagnose massive aneurysms involving most of the lateral wall, the posterior wall, or apex of the left ventricle. Massive aneurysmal involvement of the left ventricle may simulate simple left ventricular hypertrophy. The posterior wall is poorly contrasted with mediastinal structures so that aneurysm in this location is difficult to demonstrate. Displacement of a barium-filled esophagus may be helpful.[11] Similarly, the cardiac apex is surrounded by structures which obscure its visualization; production of a gas bubble in the stomach with effervescent materials may

give sufficient contrast to demonstrate an aneurysm at the apex of the heart. Roentgenkymograms permit detailed study of pulsations. Angiocardiography may demonstrate an aneurysmal bulge if a mural thrombus is not present.

THE ELECTROCARDIOGRAM

In the past a variety of electrocardiographic patterns have been offered as characteristic or at least suggestive of ventricular aneurysm. The fact that there has been dispute about the existence of a characteristic pattern is good evidence that there is none. Published electrocardiograms consisting of at least 3 standard, 3 unipolar extremity, and 6 precordial central terminal leads from 16 patients with ventricular aneurysm have been reviewed and are supplemented by similar tracings from 13 cases reported here.

Standard lead patterns alone have not proved reliable, either for detection of the presence of myocardial infarction or for illustrating suggestive residual changes. Patterns associated with ventricular aneurysm have been described in terms of the direction of the main QRS deflection in the 3 standard leads, particularly the presence of a deep S wave in Leads II and III.[1,6,24,25] Deviation of the electrical axis toward the right has been observed frequently in spite of obvious enlargement of the heart to the left.[7,24,26,27] Master[8] noted the presence of intraventricular block with a deep Q wave and inverted T in standard Lead I in one-third of his patients with aneurysm of the anterolateral surface of the left ventricle and felt that this should suggest the diagnosis. Since the standard lead patterns described have been variable with no set pattern significantly consistent, and since these patterns may be present with myocardial infarction in the absence of an aneurysm, many have stated that there is no typical electrocardiogram for ventricular aneurysm, but that any changes present are due to myocardial infarction.[5,7,9,23]

Goldberger and Schwartz[28] and Goldberger[29] have reaffirmed the lack of specificity in several standard lead patterns. The presence of an R wave in the right arm lead in all patients with ventricular aneurysm studied by these authors has led to the impression that absence of a tall R_{AVR} after infarction of either the anterior or the posterior wall is presumptive evidence that ventricular aneurysm is absent. Goldberger has pointed out that the R_{AVR} may also be present with myocardial infarction in the absence of an aneurysm of the ventricle. According to Goldberger, the upward deflection in the right arm lead indicates either a marked clockwise rotation of the heart around its longitudinal axis or posterior displacement of the cardiac apex, both of which would result in reflection of epicardial potentials from the posterobasal portion of the left ventricle toward the right shoulder. With a QR or predominantly upright complex in the right arm lead and a Q wave in the left arm lead, as is registered when infarcted anterolateral myocardium faces the left shoulder, the presence of both right axis deviation and the various standard lead patterns is explained. Again it should be pointed out that findings such as these are not limited to ventricular aneurysm and may be present with myocardial infarction alone.

Although Goldberger has not described cases of ventricular aneurysm without a relatively tall upward deflection in the right arm lead, a review of

3 published tracings has failed to reveal such a complex.[11,30,31] It is therefore evident that absence of a tall R_{AVR} does not rule out ventricular aneurysm.

Elevation of the RS-T segment persisting long after the acute phase of myocardial infarction and in association with aneurysm of the left ventricle has been noted for many years.[3,12-14,23,25,29-35] While this feature is now frequently regarded as being highly suggestive of ventricular aneurysm, an explanation for its presence has been missing until recently. Myers and his group[14] have pointed out that in leads over completely infarcted muscle the potentials registered are those of the underlying ventricular cavity, unmodified by the infarcted wall which is unable to develop potentials. Such potentials are reciprocal to those found in epicardial leads or leads taken over uninvolved muscle of the same ventricle, usually from the opposite wall. In the presence of an infarct large enough to give rise to a ventricular aneurysm, hypertrophy of the remaining myocardium usually occurs, leading to a greater RS-T segment elevation within the ventricular cavity. Thus, there are 2 factors to account for permanent RS-T elevation: (1) lack of modifying potential from completely infarcted muscle, and (2) hypertrophy of the opposite wall. It is also apparent that persistent RS-T elevation is not limited to ventricular aneurysm; it may be present whenever there is extensive destruction and fibrosis. Ventricular aneurysms usually develop in such extensive myocardial infarcts.

Summarized in Table I are the characteristics of illustrated electrocardiograms from 16 published cases of chronic ventricular aneurysm. Consideration has been given to the location of the infarcted and aneurysmal area, defects in conduction, RS-T segment displacement, evidence of hypertrophy of intact myocardium, and age of the infarct. Only tracings consisting of at least the 3 standard leads, 3 unipolar extremity leads, and the usual 6 precordial central terminal leads have been considered. It is evident that these aneurysms involve usual portions of the myocardium, the majority being apical or anterolateral. Delayed intraventricular conduction was present in 10; in 8 of these, the conduction defect could be localized to the free wall of the left ventricle ("arborization block") and was undoubtedly in the infarcted portion of the heart wall. The other 2 showed right bundle branch block. Persistent elevation of the RS-T segment in leads facing the infarcted and aneurysmal area was clearly present in one-half of these patients; in the remainder elevation was either borderline or absent. Dome-shaped RS-T segments or abnormal T waves along with QRS changes pathognomonic of infarction were present in all of these patients. In an effort to account for persistent RS-T segment elevation, a search was made for evidence of hypertrophy of the uninvolved myocardium. This was not always possible electrocardiographically, depending largely upon cardiac position and the type of complex registered in the usual leads. However, there was evidence in 7 of these cases of hypertrophy of the opposite wall of the heart.

In the remainder either autopsy data was inadequate or illustrative leads did not show complexes from the intact left ventricular myocardium, usually the posterior wall. Since these were old infarcts, elevation of the RS-T segment cannot be explained on the basis of "current of injury."

TABLE I. SUMMARY OF ELECTROCARDIOGRAPHIC CHANGES FROM 16 PUBLISHED ILLUSTRATIONS IN CASES OF VENTRICULAR ANEURYSM UTILIZING UNIPOLAR EXTREMITY AND AT LEAST 6 "V" PRECORDIAL LEADS IN ADDITION TO STANDARD LEADS

AUTHORS	LOCATION OF INFARCT AREA (BY ELECTROCARDIOGRAM OR AUTOPSY)	SEPTAL AND VENTRICULAR CONDUCTION	RS-T SEGMENT (ESTIMATE OF ELEVATION AND SHAPE)	EVIDENCE OF HYPERTROPHY OF INTACT MYOCARDIUM	AGE OF INFARCT
Myers and associates[31]	Case 95 Posterolateral at base	QRS: 0.13 second; left ventricular conduction defect	Slightly elevated in aV_F and in II and III	Anterior wall; in V_2 to V_4 relatively tall R and depressed RS-T; hypertrophy at autopsy	Old, total duration unknown
Myers and associates[30]	Case 56 Old infarct of apical one-half of anterior wall with aneurysm; recent posteroapical infarct	Normal	Elevated up to 2 mm.; straightened in V_4; isoelectric (but cove-shaped T) in II, III, and aV_F		Old: anterior with aneurysm; recent: posterior
Myers and associates[14]	Case 44 Anterolateral at apex	Normal	Isoelectric but dome-shaped in V_3 to V_6		Old, total duration unknown
	Case 46 Apical and anterolateral; intramural (lateral)	QRS: 0.15 second; left ventricular conduction defect	Elevated up to 2 mm.; straightened in V_4 and V_5	Uninfarcted myocardium, mostly posterior wall; heart weighed 744 grams	Old, probably 2 years
	Case 47 Apical and anterolateral	Normal	Elevated up to 2.5 mm.; dome-shaped in V_2 to V_6 with cove inversion of T		Old: anterolateral at apex with aneurysm; recent patchy higher: anterolateral
	Case 48 Anterolateral with anterior aneurysm	Normal	Elevated up to 5 mm.; concave upward in V_2 to V_6	Posterolateral wall; hypertrophy at autopsy	Old, calcified
	Case 50 Apical and anteroseptal	QRS: 0.12 second (estimated); left ventricular conduction defect	Elevated up to 3 mm.; concave upward in V_2 and V_3; dome-shaped in V_4 to V_6	Lateral and posterior wall; heart weighed 570 grams; tall R in aV_L; horizontal heart	More than 2 years
Wolff[35]	Fig. 93 Anterolateral	QRS: 0.13-0.14 second; left ventricular conduction defect	Elevated up to 3 mm.; concave upward in V_1; dome-shaped in V_2; straightened in V_3 to V_6		6 years
Wolff[35]	Fig. 94 Anteroposterolateral	QRS: 0.12 second (estimated); left ventricular conduction defect	Elevated up to 1 to 2 mm.; concave upward in V_2; straightened in V_3 to V_6 and aV_L		1 year

TABLE I.—Cont'd

AUTHORS	LOCATION OF INFARCT AREA (BY ELECTRO-CARDIOGRAM OR AUTOPSY)	SEPTAL AND VENTRICULAR CONDUCTION	RS-T SEGMENT (ESTIMATE OF ELEVATION AND SHAPE)	EVIDENCE OF HYPERTROPHY OF INTACT MYOCARDIUM	AGE OF INFARCT
Wolff[35]	Fig. 36 Anteroseptal	Right bundle branch block	Elevated up to 2 mm.; concave upward in V_1 and V_2; straightened in V_3; dome-shaped in V_4		1½ years
Wilson and co-workers[12]	Fig. 25 Anterolateral	QRS: 0.10-0.12 second (estimated); incomplete right bundle branch block	Elevated to 3.5 mm.; concave upward in V_2; dome-shaped in V_3 to V_6 (slightly greater elevation after 6 mo. interval)		1 year
Goldberger[29]	Fig. 123 Anterolateral	Normal	Elevated up to 3 mm.; concave upward in V_2 and V_3; dome-shaped in V_4 to V_6		6 months
Caplan and Sherwood[11]	Case 1 Anterolateral	Normal	Elevated up to 2.5 mm.; straightened in V_2; dome-shaped in V_3 to V_6	Posterior wall (?) (left leg-vertical heart); depressed RS-T; delayed R	More than 2 years
	Case 2 Anterolateral	QRS: 0.12 second (estimated); left ventricular conduction defect	Elevated up to 1 mm.; concave upward in V_2 to V_4; dome-shaped in V_5 and V_6 and left arm		1 year
Rosenberg and Messinger[31]	Case 1 Anterolateral	QRS: 0.11-0.12 second (estimated); left ventricular conduction defect	Elevated up to 2 mm.; concave upward in V_2 to V_3; dome-shaped in V_4 toV_6	Lateral wall (aV_L-horizontal heart); marginal subendocardial scar; tall R	More than 6½ years
	Case 2 Anterolateral	QRS: 0.12 second (estimated); left ventricular conduction defect	Elevated up to 2 mm.; straightened in V_2 and V_3: dome-shaped in V_4 to V_6 and aV_L	Posterior wall; deep S in V_1	Old

ILLUSTRATIVE CASES

The following brief case report illustrates the important clinical features of ventricular aneurysm associated with a large, anterolateral myocardial infarction.

CASE 1.—J. B., a white man, 62 years old, was admitted to the hospital in 1947 with a history of effort angina for 4 years and, finally, a month before admission, severe prolonged precordial

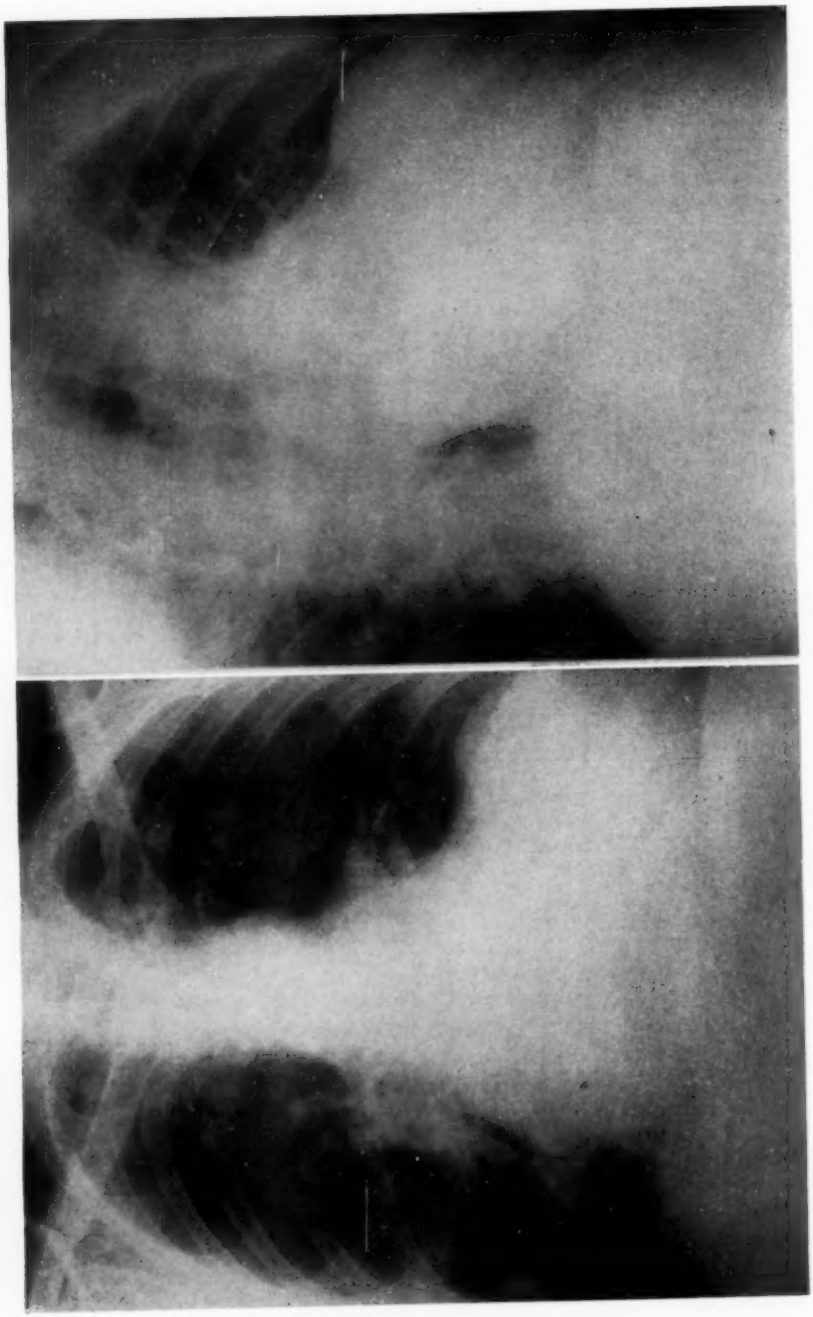

Fig. 1 (Case 1).—Posteroanterior and right anterior oblique chest films showing anterolateral aneurysm.

pain with acute dyspnea. He saw his private physician repeatedly during the next month but was not put to bed. Because of continuing episodes of substernal pain and dyspnea, the patient was admitted to this hospital. There were no remarkable findings on examination except for distant heart tones. Since the sedimentation rate was elevated and the electrocardiogram revealed an extensive anterolateral myocardial infarct with RS-T elevation and deep cove inversion of T waves over the infarcted area, the patient was kept at bed rest and given anticoagulants. During the next few months, the patient was symptomatically improved, but the cardiac apical impulse moved outward. Cardiac glycosides have since been used continuously. Serial electrocardiograms showed regression of the T-wave inversion but persistent elevation of the RS-T segment. The first chest roentgenogram was taken 2 months after admission and revealed a large aneurysm of the anterolateral wall of the left ventricle which has not changed significantly

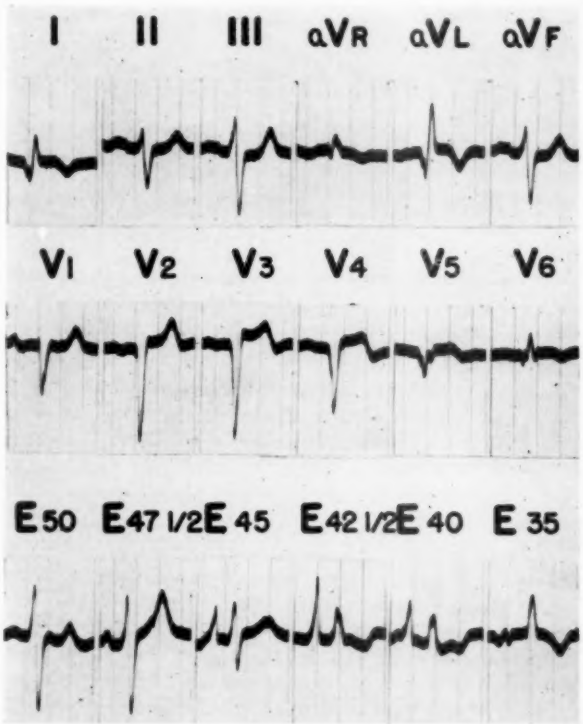

Fig. 2 (Case 1).—Electrocardiogram. See text.

since then (Fig. 1). Systolic expansile pulsation of the aneurysm was demonstrable on fluoroscopy and by roentgenkymogram. Three months after admission, the electrocardiogram had stabilized and has since remained unchanged except for development of progressive prolongation of the QRS interval which was first recorded a year after admission to the institution. Since March, 1949, the QRS interval has remained at 0.16 second (Fig. 2). The conduction delay is in the free wall of the left ventricle rather than in either bundle branch. The initial deflection in all left ventricular leads is clearly a Q wave, and there has been no change in the shape of the ventricular complexes from the time of normal conduction time. Persistent RS-T elevation was shown in all leads over infarcted muscle (V_2 to V_6 and aV_L); no greater elevation was found in high precordial leads (not illustrated). Upward concavity was clearly evident, especially in those leads showing the greatest elevation of RS-T. These leads were most directly opposite the posterior wall and in this case were believed to show the reciprocal pattern of hypertrophy of the intact posterior wall. Esophageal leads were obtained in an effort to demonstrate posterior wall hypertrophy.

However, at ventricular levels (E 50 and E 47½) the complexes were of right ventricular or posterior transitional origin. At auricular levels (E 45 and above) the posterior left ventricular vector was directed upward, producing a complex much like those registered at the right shoulder (aV_R) where an upright complex was seen. This is interpreted as posterior displacement of the cardiac apex with rotation about the transverse axis so that the right shoulder "looks at" the posterobasal portion of the left ventricle. It seems reasonable to assume that the large anterolateral aneurysm had pushed the apex posteriorly. This patient continues to be ambulatory but has poor capacity for exertion 2½ years after the onset of myocardial infarction. Visible prominence of the left anterior chest wall has appeared during this interval although the size of the aneurysm is essentially unchanged.

The following 4 autopsied cases serve to illustrate variations in the electrocardiographic patterns associated with chronic ventricular aneurysm.

CASE 2.—G. LeC., a 62-year-old white man, gave a classical history of myocardial infarction 3 years prior to admission. He remained in bed 1 week, then resumed his usual activities without further cardiac symptoms. At the time of admission he sought attention for symptoms ascribed to hemachromatosis. Impaired carbohydrate tolerance had been discovered 16 years previously for which a diet and insulin were prescribed. During this hospital admission cardiac glycosides were not used. Three weeks after admission the patient died of bleeding esophageal varices. The heart showed an old occlusion of the anterior descending coronary artery with an old infarction of the apical portion of the interventricular septum and anteroseptal wall at the apex. The aneurysm measured 2.5 by 6 cm. and was mainly in the interventricular septum at the apex, giving rise to a bulge into the right ventricular cavity. There was hypertrophy of the intact left ventricular myocardium.

The electrocardiogram is reproduced in Fig. 3,*A*. Features diagnostic of septal infarction[36] were QS complexes in V_1 and V_2 with definite slurring of the descending limb, requiring 0.05 to 0.06 second to reach the nadir, with associated dome-shaped and slightly elevated RS-T segments. From the intrinsicoid deflection of the P wave in V_1, it was apparent that the lead overlaid the right atrium and thereby faced the right side of the interventricular septum. Lead V_3 showed a tiny Q, tiny R, and relatively deep S with the same abnormal RS-T and T. The complexes in the remaining precordial leads were of left ventricular origin and were relatively normal except for marginal zone changes in the T wave in V_4. Conduction time was within normal limits, there being no extensive involvement of the bundle branches or Purkinje network. This electrocardiogram was characteristic of septal infarction without disturbance of bundle branch conduction. Except for slight RS-T elevation which was associated with fairly large transmural myocardial infarction with hypertrophy of the intact myocardium, there was nothing characteristic of ventricular aneurysm.

CASE 3.—F. M., a 62-year-old white man, was admitted to the hospital in congestive heart failure of insidious onset which began shortly after a sensation of chest compression 9 months before admission. Cardiac glycosides had improved his symptoms and were in use on admission. With further cardiac measures, the patient again improved until sudden death 6 weeks after admission. At autopsy the heart weighed 735 grams. There was an old thrombus in the left anterior descending coronary artery and a large old infarct of the apex and interventricular septum with aneurysmal dilatation of the total infarcted area. The aneurysm extended 9 cm. up the interventricular septum and 6 cm. up the anterolateral wall (apical one-half) of the left ventricle.

An electrocardiogram (Fig. 3,*B*) taken 1 month before death was unchanged from a tracing taken a week earlier. The large septal and anterolateral infarct was well shown in the precordial leads with slurred and notched QS complexes in V_1 to V_5. RS-T segment elevation was shown in V_2 to V_6; these were straightened or upwardly concave in V_2 to V_4 and rounded in V_5 and V_6. Since there was considerable destruction of the lateral ventricular wall in this patient, the changes associated with hypertrophy were not shown reciprocally in V_1; hypertrophy of the posterior wall, however, was well shown reciprocally in V_2 to V_4, leading to a persistent elevation of RS-T with upward concavity or straightening. As pointed out previously, the changes were those of a

massive transmural infarct underlying the exploring electrode and had no relationship to ventricular aneurysm except that aneurysm can be expected to develop in such an extensively damaged myocardium.

CASE 4.—F. T., a 58-year-old Negro man, gave an inadequate history and was admitted to the hospital with congestive heart failure and bronchopneumonia. Following a good response to

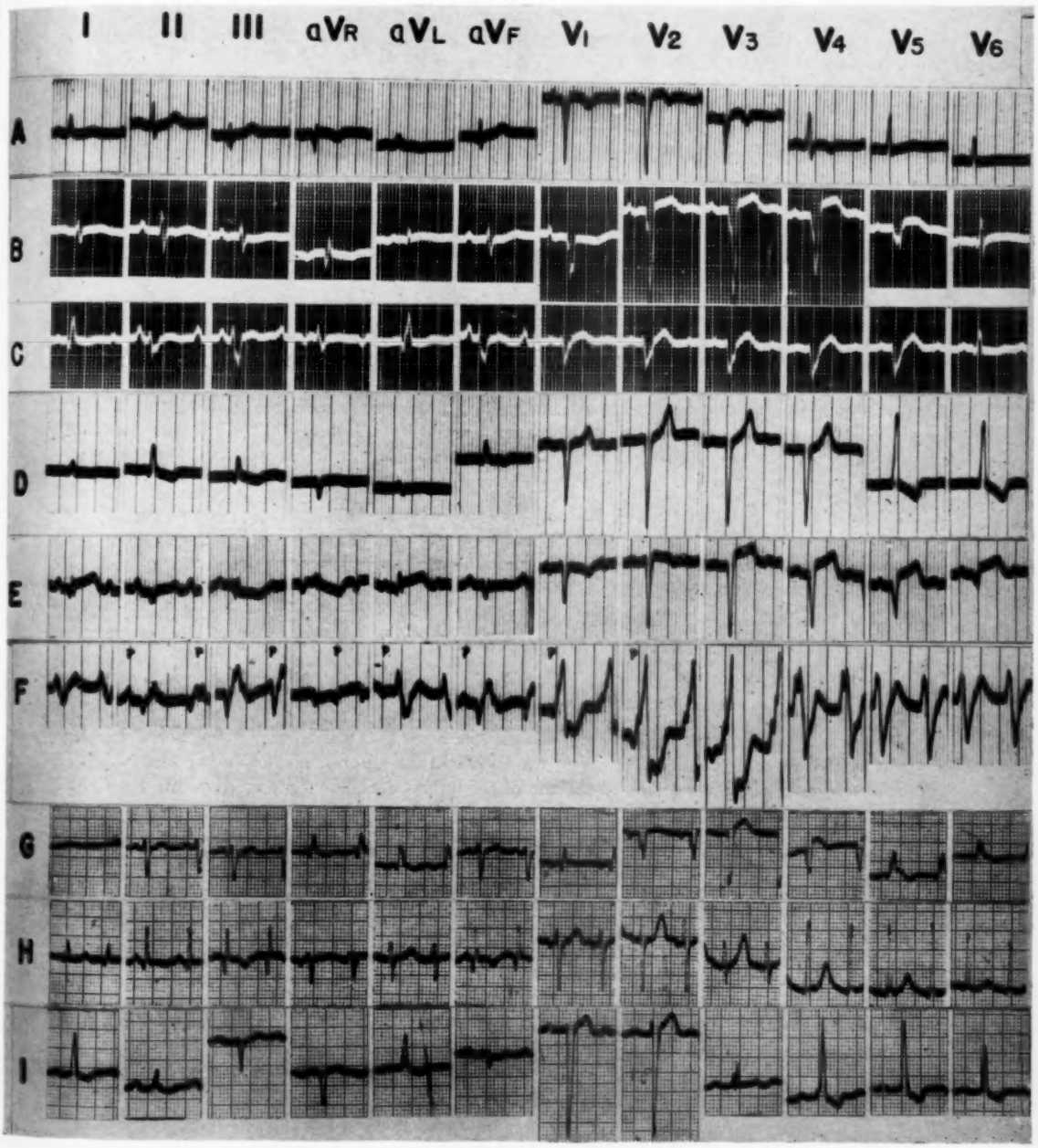

Fig. 3.—Electrocardiograms. *A*, Case 2; *B*, Case 3; *C*, Case 4; *D*, Case 5; *E*, Case 6; *F*, Case 7; *G*, Case 8; *H*, Case 9; and *I*, Case 10.

treatment, edema eventually returned, and the patient died 2 months after admission in cardiac failure. At autopsy there was a large anterolateral ventricular aneurysm with calcification of the wall. The aneurysm was in an area of old myocardial infarction which extended from 4 cm. below the base of the heart to the apex.

The electrocardiogram (Fig. 3,*C*) did not reveal the infarct because of left bundle branch block. The QRS interval was 0.12 second. Lead V_7 or V_8 should have been taken to be certain of the conduction defect; however, a tiny R appeared to precede the downward deflection in V_6 and aV_L and correlated with activation of the septum from right to left. The intrinsicoid deflection was delayed to 0.09 second in V_6 and aV_L.

CASE 5.—L. B., a 56-year-old white man, was first admitted to the hospital in 1941, following a cerebrovascular thrombosis. There was known hypertension for 5 years but no history suggestive of myocardial infarction. Cardiac enlargement and auricular fibrillation were found, but the patient was compensated. No cardiac glycosides were given. Four years later, the patient was readmitted for symptoms ascribed to gastric ulcer with recent onset of congestive failure and died 2 weeks later after rupture of the gastric ulcer. The heart showed marked left ventricular hypertrophy and old fibrosis of the apex, extending from the anteroseptal wall posteriorly through the interventricular septum to involve the posterior wall at the apex of both left and right ventricles. There was a small aneurysm of the posteroseptal portion of the right ventricle in the infarcted area.

An electrocardiogram in 1941 (Fig. 3,*D*) was not greatly different from that of 1945 which did not include a full set of precordial leads. The tracings showed auricular fibrillation, left ventricular hypertrophy, and the anteroposterior myocardial infarct. Anteroseptal infarction was shown in V_2 and V_3 by QS complexes which replaced the RS complexes of V_1. Involvement of the posterior wall of the left ventricle as well,[30,34] with the heart in semivertical position, was suggested in aV_F by a shallow Q followed by a slurred R. There are no known criteria to reveal the right ventricular infarct or aneurysm.

Electrocardiograms from the following 4 cases are illustrated in Fig. 3,*E* to *H*. These are from patients with recent myocardial infarction. Since RS-T segment elevation has not been established as permanent, attention would not be drawn to the possibility of ventricular aneurysm from the electrocardiographic standpoint alone.

CASE 6.—F. V., a 50-year-old white woman, died 11 days after the onset of myocardial infarction which was complicated by severe gastric dilatation and hemorrhage. The heart showed a recent large infarct of the anterior wall at the apex and the anterior portion of the septum with aneurysmal protrusion of the infarcted portion of the interventricular septum 3 cm. into the right ventricular cavity. Three electrocardiograms were obtained and were similar except for slight progressive downward displacement of the elevated RS-T segments. The tracing on the day of death (Fig. 3,*E*) showed changes of an anterolateral infarct, but except for T-wave abnormality in leads over the right ventricle (V_1 and V_2), it did not suggest infarction of the septum. The initial R deflection in these leads must have been derived from activation of the intact portion of the septum and the right ventricle. In this case it was not possible to suspect infarction or aneurysm of the interventricular septum.

CASE 7.—L. M., a 57-year-old white man, was known from previous study to have a posterior scar from myocardial infarction. Two weeks following readmission for a recurrence of myocardial infarction, the patient died. A 6-foot projection film of the chest, shortly before death, revealed a marked bulge of the left border of the heart. No autopsy was obtained. An electrocardiographic diagnosis of infarction was not possible because of the presence of variable ectopic ventricular rhythms. The tracing illustrated (Fig. 3,*F*) was obtained 2 days before death and showed interference dissociation with an auricular rate of 84 per minute and a ventricular rate of 120 per minute.

CASE 8.—A. W., a 62-year-old white man, died in cardiac failure which began insidiously about 2½ months earlier without symptoms suggestive of coronary occlusion. At autopsy there was an extensive anteroseptal infarct which appeared to be about 2 months old with destruction of most of the anterior wall and aneurysmal dilatation of the infarcted area. An electrocardiogram was obtained 4 days prior to death (Fig. 3,*G*) and clearly revealed the myocardial infarct. Since only 1 tracing was obtained, any persistence of RS-T elevation is not known. No conclusions can be reached as to whether the existing pattern might at least suggest the possibility of ventricular aneurysm.

CASE 9.—W. P., a 68-year-old white man, was admitted to the hospital acutely ill with an incomplete history and died the next day. Symptoms and findings were those of acute myocardial infarction. At autopsy there was an old and recent infarct of the posterobasal left ventricular myocardium plus an area of old scarring in the apical portion of the septum. The aneurysm involved the posterobasal portion, which included a small portion of the adjacent interventricular septum and extended into the posterolateral wall, measuring 7 by 7 cm. The recently infarcted portion appeared to be about 2 weeks old. The electrocardiogram (Fig. 3,*H*) was diagnostic of posterior infarction but gave no indication of the age, since there was neither elevation of RS-T in aV_F nor reciprocal depression in precordial leads. While left ventricular hypertrophy existed, the electrocardiogram did not reveal this. Thus there was no reason to suspect the presence of a ventricular aneurysm.

The following is a case of mycotic or erosive aneurysm of the interventricular septum, associated with subacute bacterial endocarditis of the aortic valve. Here again the electrocardiogram would not reveal the presence of the aneurysm.

CASE 10.—A. A., a 54-year-old white man, died after an illness of 2 months, during which time the diagnosis of subacute bacterial endocarditis was suspected but not confirmed by clinical studies. Cardiac glycosides were being used. At autopsy there was ulceration of the aortic valve with a mycotic aneurysm of the interventricular septum just below. The aneurysm had ruptured into the cavity of the right ventricle. There was also a small area of thinning and fibrosis at the apical anteroseptal wall. The electrocardiogram (Fig. 3,*I*) showed only left ventricular hypertrophy plus local conduction delay, as shown by initial slurring of R in V_4 to V_6 with the intrinsicoid deflection occurring in 0.07 second. This would correlate with the apical scar rather than the septal aneurysm.

The following 3 cases suggest the importance of electrocardiography in contributing to a diagnosis of ventricular aneurysm. Each of these have electrocardiograms considered to be incompatible with the diagnosis of ventricular aneurysm as suggested by x-ray studies. Therefore, aneurysms cannot be considered proved in these patients in spite of striking x-ray changes. Each of these patients is still living without significant cardiac symptoms.

CASE 11.—F. M., a 69-year-old white man, complained chiefly of weakness, dizziness, exertional dyspnea, orthopnea, and periodic edema. The history did not suggest myocardial infarction. Presence of arterial hypertension was known 9 years earlier. Syphilis had been treated appropriately 40 years earlier in Germany. Blood pressure ranged from 130/64 to 175/110 mm. Hg; the retina showed Group 2 hypertensive changes. Mild congestive failure appeared at one time with dependent edema and hepatomegaly. Examination of the heart and lungs was not remarkable, although obesity hampered evaluation of the heart. There was evidence of peripheral neuritis involving the legs, but an incomplete pattern of tabes dorsales could not be excluded. The blood serology was negative; spinal fluid showed no evidence of syphilis but did reveal a resolving subarachnoid hemorrhage. A teleroentgenogram is reproduced in Fig. 4,*A*. Fluoroscopic study of the heart revealed the visible prominence of the left cardiac border to be primarily anterolateral in location and inseparable from the left ventricular shadow; pulsation was feeble. There has been no change in the heart silhouette for 1 year. This was considered from the roentgen

standpoint to be most likely due to an aneurysm of the left ventricle. An electrocardiogram (Fig. 4,*A*) is representative of several obtained during a year of intermittent observation. Delayed auricular conduction was shown by notched P waves, duration 0.16 second, with a P-R interval

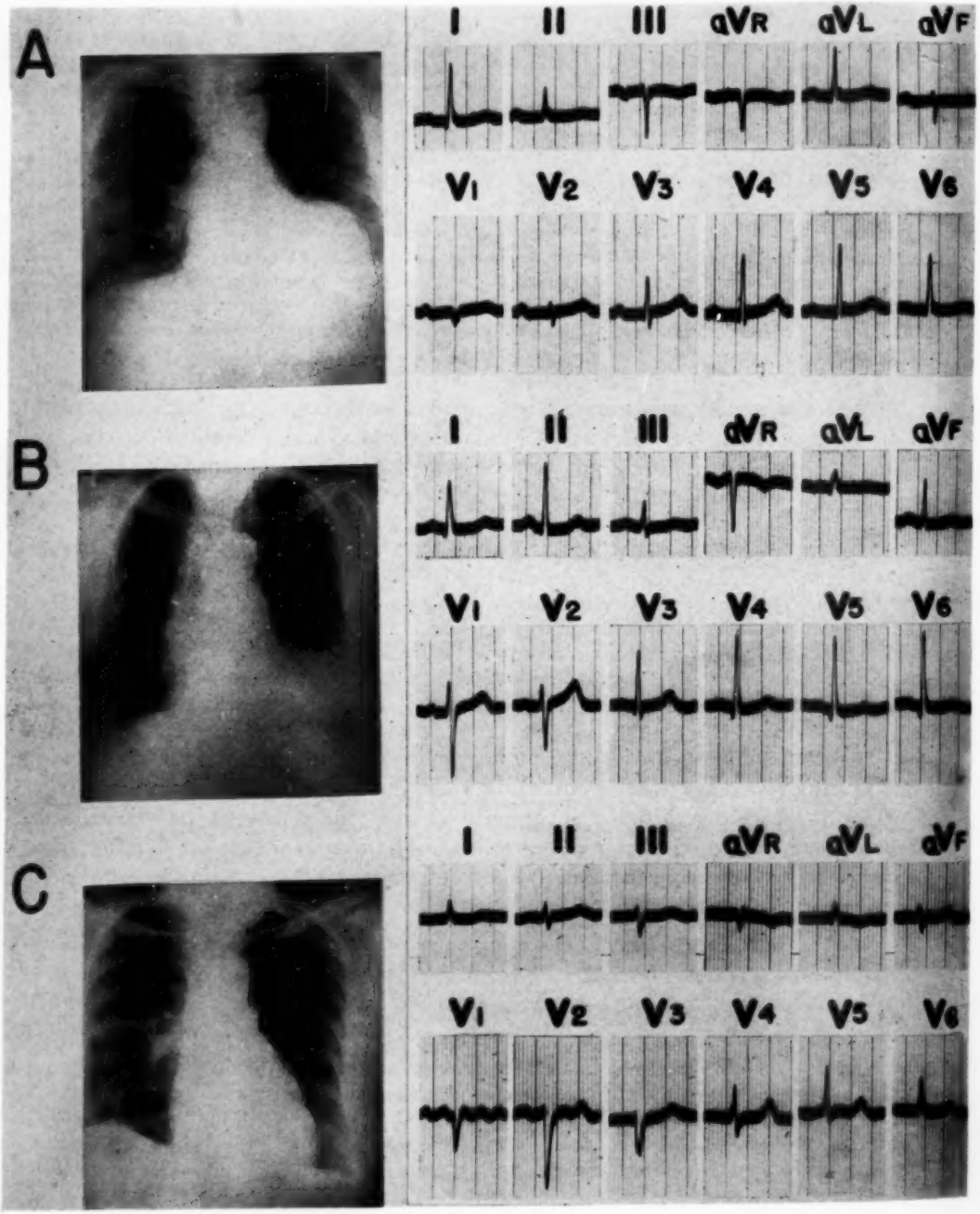

Fig. 4.—Posteroanterior chest films and electrocardiograms. *A*, Case 11; *B*, Case 12; and *C*, Case 13.

of 0.26 second. There was also delay in ventricular activation, evidenced by a QRS interval of 0.11 to 0.12 second, not due to bundle branch block. Leads further to the right (V_{3R} and V_{4R}) revealed usual right ventricular complexes, so that V_1 and V_2 showed the transitional zone. Additional leads to the left (V_7, V_8 and high precordial leads) were essentially the same as shown in V_6 and aV_L and revealed notching of the descending limb of R. Ventricular level esophageal leads (not illustrated) were of right ventricular and posterior transitional origin and thus did not give additional information about the posterior left ventricular wall. It is evident that QS complexes of transmural infarction were not present. These should be present with extensive destruction of the ventricular wall sufficient for aneurysm formation. Therefore, the roentgen-based impression of ventricular aneurysm can be seriously challenged. Gummatous myocarditis leading to aneurysm formation was considered to be a remote possibility. Since the electrocardiogram seems inconsistent and since there has been no change in the appearance of the bulge with large doses of penicillin, we feel this is not a gumma. An interesting case of possible gummatous ventricular aneurysm has been published[26]; with treatment both the abnormal ventricular bulge and abnormal T waves regressed.

CASE 12.—A. G., a 79-year-old white woman, was admitted to the hospital because of intertrochanteric fracture of the femur and has remained in the institution for 18 months. There was no history of myocardial infarction. The blood pressure has been 160 to 200/90 mm. Hg with marked atherosclerosis present. The heart was normal on physical examination except for basilar and apical systolic murmurs. The blood serologic reaction was negative. Unchanged from the initial examination are roentgenograms (Fig. 4,*B*) which showed a rounded area of increased density which could not be separated from the left ventricular border. Systolic expansile pulsation of this area was evident by fluoroscopy and roentgenkymography. The roentgen-based impression is that this is a ventricular aneurysm. A representative electrocardiogram, however (Fig. 4,*B*), failed to reveal evidence of myocardial infarction. Additional high precordial as well as esophageal leads (not illustrated) also did not show the changes of myocardial infarction. It was, therefore, concluded that the myocardium in the region of the abnormal bulge was reasonably normal, which would seem inconsistent with the roentgen-based diagnosis of ventricular aneurysm.

CASE 13.—L. E., an 83-year-old white woman, had been followed for 4 years in the institution. The initial admission was for infarction of the apical portion of the lower lobe of the right lung, secondary to phlebothrombosis of veins of the pelvis and legs. During excavation, abscess formation, and subsequent healing of the pulmonary infarct, chest roentgenograms repeatedly showed unusual prominence to the left ventricular border (Fig. 4,*C*) which had not changed in size or shape during a 4 year interval. The left auricle was not enlarged. Fluorsocopy of the bulging area showed systolic expansile pulsation, thus leading to the impression of ventricular aneurysm at the base of the heart. Blood serology was negative. The electrocardiogram (Fig. 4,*C*) was relatively normal except for auricular fibrillation; high precordial leads were similar to those illustrated, thus failing again to demonstrate evidence of myocardial infarction. These findings seem incompatible with the diagnosis of ventricular aneurysm.

DIFFERENTIAL DIAGNOSIS

A few conditions can be considered in the differential diagnosis of cardiac aneurysm.[9,11] Tumors of the heart and pericardium pulsate synchronously with ventricular contraction rather than being expansile in systole as are many ventricular aneurysms. Primary tumor (vascular sarcoma and hemangioma) is rare; a metastatic lesion may be suspected in the presence of a known primary malignancy when there is progressive enlargement in a deteriorating patient. The electrocardiogram may give evidence of localized pericarditis when tumor involves the epicardium. Other pericardial conditions (loculated effusion, diverticulum, hydatid, and other cysts) may give similar roentgen and electrocardiographic changes. Aneurysms of the sinus of Valsalva, coronary arteries, and descending aorta may be confused with ventricular aneurysm. Diseases

leading to pulmonary hypertension with an enlarged pulmonary conus as well as aneurysm of branches of the pulmonary artery can be distinguished by appropriate clinical and x-ray studies. Other chest tumors, including malignant growths, teratomas, and dermoid cysts, may be adjacent to the heart but can usually be separated from the ventricular border by roentgen study. A paraapical fat pad should not be confused.

CLINICAL COURSE

The prognosis with ventricular aneurysm is dependent primarily upon the condition of the remaining coronary arteries and the chance of further myocardial infarction, congestive failure, and embolism. Rupture of a chronic ventricular aneurysm is rare. Presence of more than one ventricular aneurysm does not change the prognosis.[5] Many authors[3,5-7,11,15,21,33] feel that the life span is no different in the presence of ventricular aneurysm. Schwedel[21] stated that "the course is that of hypertensive or arteriosclerotic heart disease unaltered by the ventricular aneurysm." Dressler and Pfeiffer[6] emphasized the work capacity of some of these patients. Satisfactory cardiac function for many years in the presence of a cardiac aneurysm is well established.[37-40]

COMMENT

While the clinical course following development of a chronic ventricular aneurysm may be essentially that of uncomplicated myocardial infarction, it is evident that there is a high correlation between aneurysm and inadequate bed rest after infarction. This has been recognized by others and is particularly clear in the present series. Recent emphasis for early ambulation would seem to ignore this possible result. Many patients, however, will have suffered "silent" myocardial infarction and will present themselves for treatment of congestive failure of insidious onset. Hypertension has been found to be present in up to one-half of the patients with ventricular aneurysm and may be important in the pathogenesis.

Some unusual locations and types of ventricular aneurysm are included in the present series. There are no known methods for the diagnosis of aneurysm involving the interventricular septum (Cases 2 and 6), although presence of myocardial infarction involving the septum may become evident electrocardiographically. Although the septum significantly encroached upon the cavity of the right ventricle in these cases, Bernheim's syndrome did not develop. There was one patient with aneurysm of the posterior wall of the right ventricle at the apex, associated with infarction of the apical portion of the left ventricle and interventricular septum (Case 5). Case 10 was one of mycotic aneurysm of the interventricular septum with rupture into the right ventricular cavity, associated with subacute bacterial endocarditis of the aortic valve.

There is ***no*** electrocardiographic pattern characteristic of ventricular aneurysm. Standard lead patterns are not consistent. Prominent upright deflection in the right arm lead is not invariably present. Delayed ventricular conduction due to interruption of the Purkinje network in an area of extensive in-

farction is not limited to ventricular aneurysm, but occurs frequently. Persistent RS-T elevation in association with QRS changes diagnostic of myocardial infarction has been offered as a pattern at least suggestive of ventricular aneurysm. Such a pattern is not limited to ventricular aneurysm and may be found with uncomplicated large myocardial scars when there is extensive destruction of the myocardial wall. Cardiac aneurysms tend to develop in such large areas of myocardial destruction. Elevation of RS-T persisting long after the stage of injury is the result of hypertrophy of the opposite wall of the heart with lack of modifying effects from the underlying destroyed myocardium.

Three cases are presented (Cases 11, 12, and 13) which combine relatively normal electrocardiograms with unusual contours involving the heart; these are thought from roentgenologic studies to be examples of ventricular aneurysm. However, failure to demonstrate electrocardiographically the changes of myocardial infarction would seem to lend serious doubt to that diagnosis.

The prognosis is not always bad, as many have thought. Many years free from cardiac disability may be attained. Rupture of a chronic cardiac aneurysm is infrequent. It is felt that the life span is no different from that of patients with myocardial infarction uncomplicated by presence of ventricular aneurysm.

SUMMARY

1. Twenty cases with autopsy or x-ray diagnoses of ventricular aneurysm have been reviewed.

2. Electrocardiographic considerations based upon the Wilson concepts from 13 cases, in addition to 16 reported elsewhere, suggest that there is no pattern characteristic of ventricular aneurysm.

3. Electrocardiographic changes, when present, are those of antecedent extensive myocardial infarction and do not differ from similar cases uncomplicated by ventricular aneurysm.

4. Persistent RS-T elevation, frequently associated with ventricular aneurysm, correlates with large infarcts which are potential sites for aneurysm formation. RS-T elevation is due to: (a) hypertrophy of the opposite heart wall, and (b) lack of modifying potential from destroyed myocardium.

5. Failure to verify presence of extensive myocardial infarction by electrocardiogram in the presence of abnormal bulges on the cardiac silhouette by roentgen study does not exclude, but should cast serious doubt, on the diagnosis of ventricular aneurysm.

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THE primary and some of the secondary branches of the arteries of the heart form a network on the outer surface of the myocardium. From this superficial network a number of more or less perpendicular branches arise to penetrate the heart muscle and to link up with a deep, subendocardial net of small arteries. The variations in the number, distribution, and branching of the coronary arteries have been the subject of a number of exhaustive studies,[1-5] and it would appear that little new could be added to our knowledge of this subject. It was noted, however, that the superficial arteries, whose normal course is through the epicardial fat, do on occasion dip into the cardiac muscle for a varying distance. This "vertical" variation in the course of the main coronary arteries is the subject of this paper, and it is proposed to refer to such arteries as "mural" coronaries. There is little mention of this phenomenon in the relevant literature, and apparently no detailed study of its frequency and distribution has ever been undertaken. Crainicianu[3] referred to the phenomenon: "Sometimes however, I was able to observe how for example the Ramus descendens of the left coronary artery, after a variable course, digs itself more or less deeply into the cardiac muscle along the course of the interventricular groove to reappear on the surface after a few centimetres. In such a case I have asked myself what influence muscular contractions may have on the circulation in a big artery which finds itself in such an anatomical position." His paper did not, however, attempt to answer the question.

Spalteholz[1] mentioned the fact in the following terms: "Not only arteries of small or medium calibre but frequently even long stretches of the big arteries disappear, in the course of growth, partly under the superficial layers of the musculature and are, in the adult, hidden under a layer of muscle which may occasionally be of considerable depth." This very definite statement (which Spalteholz made to explain the greater ease with which the superficial network can be visualized in the newborn) was, however, not followed up either by instances or by any serial analysis. His contention that the intramuscular position of part of the superficial arterial net is a postnatal development is neither borne out nor refuted by the investigation here reported, as a sufficient number of young hearts have not been examined, but one or two relevant observations on this point will be made in the course of this presentation.

Banchi,[1] Gross,[2] and Ehrich, de la Chapelle, and Cohn[5] did not mention the phenomenon at all, and Tandler[6] dismissed it with the following remark: " . . . only sometimes can one see a few myocardial fibres cross over them (the main coronary branches) bridge fashion."

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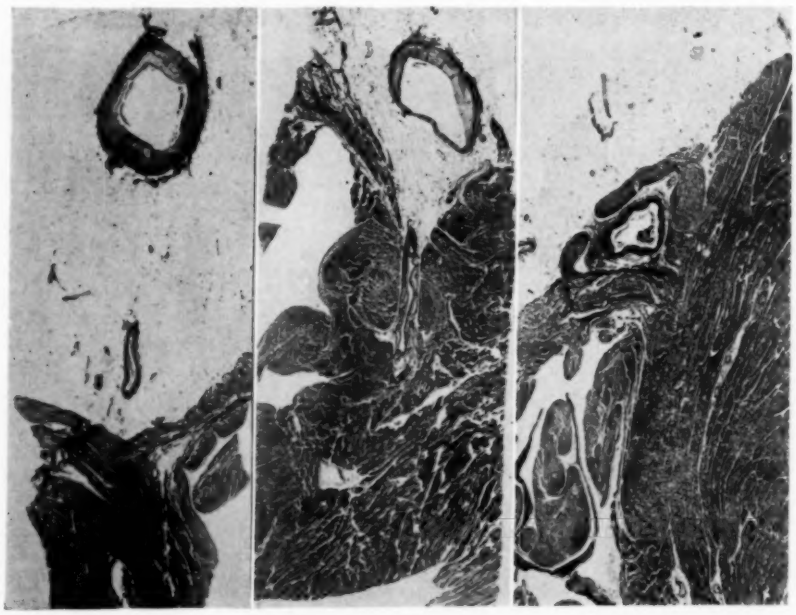
From a purely anatomical point of view, the scant attention which has been paid to the occasional intramuscular course of the main coronary branches is not surprising as it represents the type of trivial and slight deviation from the normal which we are accustomed to postulate for any part of the notoriously variable vascular system. From a pathological standpoint, however, the occurrence of this variation is of interest in that it enables us to study the influence which a muscular investment may have on the development of atherosclerosis.



A. B. C.

Fig. 1.—Anterior descending branch of coronary artery: *A*, At some distance from the interventricular groove; *B*, in the interventricular groove; and *C*, interventricular groove folded over the artery (×4).

This is the justification for this brief analysis of the occurrence of this variation and of its relation to atherosclerotic involvement. The vessel selected for this study was the anterior descending branch of the left coronary artery, because its straight course offers ease of measurement and because atherosclerotic lesions appear in it early and are clinically important. It must be understood, however, that a dipping into the myocardium is observed on occasion in all the superficial branches and is by no means confined to the anterior descending branch.

A. OCCURRENCE OF MURAL STRETCHES IN THE ANTERIOR DESCENDING BRANCH

The anterior interventricular groove of the heart usually provides a shallow bed for the left descending anterior coronary branch, although not infrequently the vessel is found to run at quite a considerable distance from this groove (Fig. 1,*A*). On other occasions, the groove may be rather deep and narrow, and the vessel may run in it like a drain in a trench (Fig. 1,*B*). In either case, the

artery can be approached by the removal of epicardial fat without any necessity of dividing cardiac muscle. In other words, its course is epicardial and remains so for its whole length. Where a narrow interventricular groove has become so folded over the artery as to leave only a thin septum of connective tissue linking the periarterial space with the epicardium, the artery, although still epicardial in a strictly anatomical sense, is, in fact, intramuscular from a physiological standpoint (Fig. 1,*C*), and such arteries have, in the present analysis, been classified as mural. Intermediate forms have offered difficulties in classification in a few cases, and these have been excluded from the series.

Sometimes, however, and this is especially noticeable (though not more common) in hypertrophied hearts, the artery is completely surrounded by myocardium and thus pursues a mural course for a varying distance or even for the whole of its length (Fig. 2).

Fig. 2.—Front view of heart. The epicardial fat has been removed. The probe is in the anterior descending artery which is covered by superficial myocardial fibers in its entire length.

Once attention is directed to this phenomenon it is found to be common, and in one hundred unselected autopsies at the Royal Infirmary, Edinburgh, the macroscopic incidence of this variation was twenty-three. The distance for which the vessel remains buried in the heart muscle varies from 5 mm. upward, and this intramuscular stretch may be interposed at any part of its course. Microscopically, it is found that the covering fibers run usually at right angles to the course of the vessel and belong to the superficial layer of the myocardium, the so-called vortex fibers (Fig. 3).[5] The perivascular space separating the muscular

investment from the adventitia may be very narrow (Fig. 3,*A*) or very wide (Fig. 3,*C*). No significant age or sex incidence was discovered.

The left anterior descending coronary artery often divides near its origin into two parallel branches, and on such occasions it often happens that one of these runs in the epicardium while the other pursues an intramuscular course (Fig. 4). Such cases are of special value in answering the questions posed in this paper.

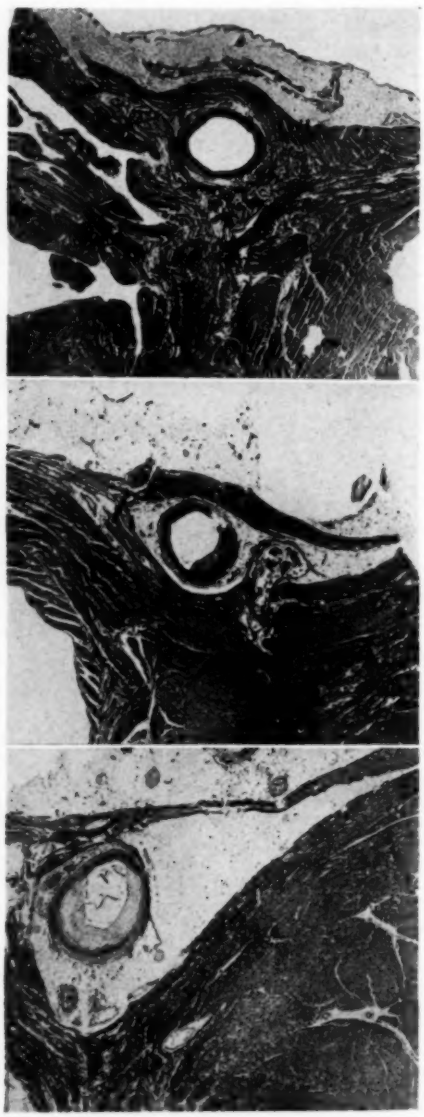


Fig. 3.—Mural coronary arteries, showing the typical arrangement of the covering vortex fibers and the variation in the width of the perivascular space (×4).

B. INFLUENCE OF MUSCULAR INVESTMENT ON ARTERIAL STRUCTURE

To determine whether the muscular investment has any effect upon the arterial wall, 100 paraffin sections of the upper third of the left anterior descending coronary branch from unselected consecutive autopsies were examined. The incidence of mural vessels was twenty-two, that is, almost the same as the macroscopic incidence. Micromeasurements of the lumen, intima, and media were taken in each case, and the average values for each vessel were tabulated. It is known that these dimensions vary with age and sex,[7] and the results were analyzed accordingly. In addition, due regard had to be paid to the difference in the caliber of the vessels, as the thickness of the wall is largely a function of the size of the lumen. Finally, the heart weight, and especially the presence of hypertension, has an important (though little recognized) influence on the configuration

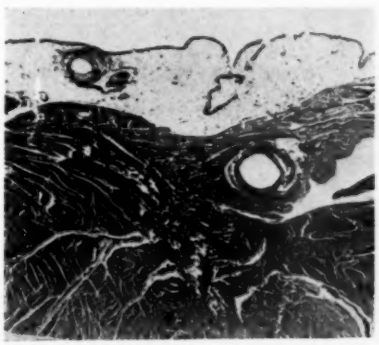


Fig. 4.—Mural anterior descending coronary branch with an epicardial collateral. The latter, though smaller, has thicker walls (×4).

and thickness of the coronary walls, and this, too, was allowed for. From the accompanying tables, it can be seen that when full allowance is made for these factors, mural stretches of the left anterior descending branch tend to have a considerably narrower intima than the epicardial stretches. In other words, at the same age and sex, in hearts of the same weight, an epicardial left anterior descending artery of the same lumen as a corresponding mural branch tends to have a considerably thicker intima. This point is well brought out by a study of the five slides in which a mural and epicardial coronary coexisted at the same level (Table I).

Taking the averages of all readings, the following ratios for the average mural and epicardial vessels were obtained: mural: lumen, 100, intima, 11.6, media, 8.4; epicardial: lumen, 100, intima, 18.3, media, 8.4; that is, other things being equal, the wall of an epicardial coronary is 33 per cent thicker than that of a mural coronary, the increase being due to intimal hyperplasia. The detailed measurements are given in Tables II and III.

TABLE I. MEASUREMENTS IN FIVE HEARTS SHOWING EPICARDIAL AND MURAL VESSELS AT THE SAME LEVEL (LEFT ANTERIOR DESCENDING BRANCH)

CASE NO.	LUMEN (MM.)		INTIMA (MM.)		MEDIA (MM.)		ATHEROMA (DEGREES)	
	EPICARDIAL	MURAL	EPICARDIAL	MURAL	EPICARDIAL	MURAL	EPICARDIAL	MURAL
580/47	1.4	1.1	0.214 0.858	0.071 0.286	0.143	0.1	4	0
204/48	0.88	1.25	0.014	0.05	0.071	0.08	0	0
423/47	1.1	1.75	0.143 1.286	0.1 0.639	0.1	0.143	3.5	3.5
248/48	0.6	0.7	0.143	0.062	0.08	0.1	1	0
409/47	1.15	1.75	0.1 0.5	0.143	0.1	0.143	2	0
Average	1.02	1.31	0.407	0.193	0.099	0.113	2.1	0.7

The slightly narrower media in the epicardial vessels of the patients in this small series is explained by the smaller lumen. The difference in intimal thickness and degree of atheroma is all the more striking.

C. RELATIVE INCIDENCE AND SEVERITY OF ATHEROSCLEROSIS IN INTRAMURAL STRETCHES

The degree of atherosclerosis was noted in each slide according to an arbitrary scale (from 0 = no lesions to 5 = severe, necrotic lesions). It may be noted here that purely fibrous intimal thickenings, which had already been given expression in the measurements of Section B, were not classified as atherosclerosis; the term was restricted to intimae showing evidence of fatty degeneration. The results of this grading are shown in Table IV. The difference here is so marked as not to be in need of further statistical analysis.

It is quite clear that mural stretches of the left anterior descending coronary branch are only rarely affected by atherosclerosis, in contradistinction to comparable epicardial stretches where this is a common finding. Here again, Table I, showing the results in the five double arteries, is instructive.

DISCUSSION

The tenuousness of the muscular bridge in the newborn may have been responsible for the impression of Spalteholz that mural stretches are less common at that age. In discussing this point, one must distinguish the two morphological types of mural coronary. In the first, the intramuscular position seems due to a deepened interventricular groove having become folded over the vessel, and this type may easily be the result of postnatal growth (Fig. 1,*C*). The other, more frequent, type in which a continuous sheet of vortex fibers overlies the artery is difficult to conceive as the result of postnatal rearrangement, especially in view of the syncytial nature of heart muscle; Spalteholz's theory seems less

TABLE II. HEARTS OVER 360 GRAMS, WITH AVERAGE VALUES IN MM. OF THE LUMEN, IMTIMA, AND MEDIA ARRANGED ACCORDING TO AGE, SEX, AND RELATION OF VESSEL TO THE MYOCARDIUM

AGE GROUPS	MALE						FEMALE					
	EPICARDIAL			MURAL			EPICARDIAL			MURAL		
	LUMEN	INTIMA	MEDIA	LUMEN	INTIMA	MEDIA	LUMEN	INTIMA	MEDIA	LUMEN	INTIMA	MEDIA
— 19												
— 29							0.9	0.111	0.111			
— 39	1.75	0.387	0.181				0.75					
— 49	1.73	0.376	0.144	1.3	0.205	0.107						
— 59	1.32	0.230	0.121	1.5	0.096	0.120	0.88	0.014	0.0714			
— 69	1.57	0.614	0.143	1.1	0.179	0.100	1.35	0.369	0.143	1.66	0.052	0.143
— 79	1.55	0.464	0.132	1.3	0.402	0.104	1.7	0.464	0.132			
— 89	1.57	0.256	0.09									

TABLE III. HEARTS BELOW 360 GRAMS WITH AVERAGE VALUES IN MM. OF THE LUMEN, INTIMA, AND MEDIA ARRANGED ACCORDING TO AGE, SEX, AND RELATION OF VESSEL TO THE MYOCARDIUM

AGE GROUPS	MALE						FEMALE					
	EPICARDIAL			MURAL			EPICARDIAL			MURAL		
	LUMEN	INTIMA	MEDIA	LUMEN	INTIMA	MEDIA	LUMEN	INTIMA	MEDIA	LUMEN	INTIMA	MEDIA
— 19	1.6	0.25	0.143				1.193	0.020	0.100			
— 29				1.27	0.080	0.094	1.8	0.434	0.131			
— 39	1.117	0.650	0.118	1.25	0.101	0.071	1.75	0.143	0.127			
— 49	1.49	0.311	0.104				2.16	0.286	0.071			
— 59	1.27	0.285	0.123	1.37	0.092	0.135	1.32	0.142	0.112			
— 69	1.36	0.227	0.116				2.03	0.264	0.135	1.25	0.100	0.143
— 79	1.62	0.254	0.138	1.75	0.160	0.0355				1.33	0.142	0.071
— 89												

applicable here (Fig. 4). It would seem as if the budding coronary artery grows in these instances under or into the sheet of vortex fibers, an event which would have to be dated at about the seventh week of embryonal life.[8,9,10] On the other hand, as new formation of myocardial fibers proceeds concurrently with the formation of the coronary network,[11] the possibility of muscular overgrowth of a formed coronary branch must also be considered. How far genetic factors enter into these processes is obscure, but in other parts of the body and even in the coronary system, arterial variations have been shown to have a familial or racial incidence.[12,13]

TABLE IV. DEGREE OF ATHEROMA IN EPICARDIAL AND MURAL CORONARY SECTIONS

	EPICARDIAL		MURAL	
DEGREE OF ATHEROMA	HEARTS OVER 360 GRAMS	HEARTS UNDER 360 GRAMS	HEARTS OVER 360 GRAMS	HEARTS UNDER 360 GRAMS
5	14	3	0	0
4.5	3	1	1	0
4	2	2	1	0
3.5	4	2	1	0
3	2	1	0	0
2.5	2	2	0	0
2	2	1	0	0
1.5	0	3	0	0
1	2	3	0	0
0	13	19	9	11

To understand the effect of a myocardial investment on intimal thickness, we must recall that intimal growth is largely a postnatal phenomenon and continues in many cases throughout life. The actual thickness reached, although partly determined by sex and age, varies enormously from patient to patient and is thus clearly greatly influenced by other factors. The most important of these factors is intravascular stress, and an increase of intra-arterial tension invariably leads to intimal hyperplasia.[14] Disease or atrophy of the media is as effective in this respect as an absolute increase in blood pressure, so that overdistention seems to be the specific stimulus for intimal growth. In other words, the intima is a functional layer formed in response and as an adaptation to the mechanical stress with which the vessel has to contend. Its very existence is an expression of relative weakness of the media.

The effect of a myocardial investment is to reinforce the muscular action of the media. The myocardial fibers run at approximately right angles to the anterior descending branch and can therefore effectively control any overdistention of the vessel. Coronary dilatation tends to occur at the end of systole, that is, just when this protective action of the muscular investment would be at its height.[15] On the other hand, it might be thought that, at the height of systole, the mural artery is subjected to compression and thus to increased mechanical

stress. It has, however, been shown[16,17] that the effect of muscular contraction on an intramuscular artery is actually to open up the lumen and to facilitate blood flow. Thus, mechanical stresses are probably diminished by a mural course. In particular the effective stimulus for intimal hyperplasia, overdistention, is largely counteracted. It is interesting in this connection to recall that the hyperplastic arteriolar changes of hypertension are much less severe and much less common in the arterioles of muscles than in those of parenchymatous organs. Teleologically speaking, it would seem that intimal hyperplasia, being an internal buttressing effort against overdistention, becomes superfluous where external buttresses in the form of a muscular investment are provided.

The media is less affected by these factors. Its limits of normal variation are narrow, that is, it is genetically much more fixed than the intima. Indeed, the limited capacity of the arterial media to respond to increased stresses is the reason for intimal hyperplasia. There is, however, a limited hypertrophic response of the coronary media to suitable stresses, a hypertrophy which, at a later stage, is often followed by atrophy. Another form of medial atrophy is that occurring with extremes of intimal thickening, especially under atheromatous plaques.

The protective action of the muscular investment will express itself therefore, in the case of the media, by a lessened incidence of the extremes of hypertrophy and atrophy.

Given the fact that the mural intima is considerably narrower than the intima of epicardial vessels, the lower incidence of atheroma is not surprising. Atheroma is bound up with the development of the intima, and its frequency and severity are strictly proportional to the extent of subendothelial growth.[7,14,18] Another important consideration is that of the critical depth of the intima. The normal intima is an avascular structure, and the critical depth is that at which the intima acquires an adventitious blood supply. It varies with each vessel, being 0.5 mm. in the aorta.[14] In the coronary artery it is approximately 0.35 mm. It has become increasingly clear that the clinical significance, that is, the danger, of atheroma is bound up with disturbances of this secondary blood supply.[19,20] While 33 per cent of the epicardial arteries in this series reached an average intimal depth of more than critical value, only 14 per cent of the mural arteries did so. Thence, the danger of coronary accidents due to atheroma would appear to be more than twice as great in epicardial stretches. However, the three mural sections which displayed marked atheroma formed such a contrast to the remaining twenty in which atheroma was entirely absent as to suggest that we were probably dealing here with lesions which had not originated in the mural stretch but were an extension of thrombotically determined streaks of atheroma[21] from the epicardial part of the vessel. Accepting this interpretation, we would arrive at the conclusion that mural stretches of the anterior descending coronary artery never produce clinically significant atheroma.

It is a melancholy reflection that a shift of a few millimeters in the anatomical course of the main coronary branches would have resulted in practical immunity from the most common form of coronary vascular accident, that is, atherogenic thrombosis. This reflection gains a certain piquancy through the investigations

of Chase and de Garis[22] who found that while the gorilla and gibbon have an epicardial network of main coronaries, the coronary arteries of the chimpanzee and, to a lesser extent, of the orangutan tend to run a mural course. Using an outmoded form of expression, it would seem that, in this respect at any rate, we are descended from the wrong type of ape.

SUMMARY

1. One of every five anterior descending coronary arteries (human) runs for all or part of its course in the myocardium.

2. Such mural arteries have a considerably thinner intima than corresponding epicardial branches, and the extremes of medial hypertrophy and atrophy are found less frequently in them.

3. Atheroma occurs only rarely in these mural stretches.

4. These differences in the normal and morbid anatomy seem to be related to a medialike protective action of the surrounding myocardium.

5. The mural coronary artery provides one further example of the paramount importance of local factors in the genesis of atheroma.

The material for this investigation comes from routine autopsies at the Royal Infirmary, Edinburgh. I wish to thank Mr. T. C. Dodds of the Pathology Department of the University of Edinburgh who produced the microphotographs.

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THE NORMAL ESOPHAGEAL LEAD ELECTROCARDIOGRAM

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THE esophageal lead electrocardiogram is of increasing significance in the study and diagnosis of cardiac arrhythmias and of posterior myocardial disease. This is especially true in instances of the former in which definite evidence of atrial activity cannot be seen clearly in the standard or unipolar limb and precordial leads; it is true in instances of the latter in which customary leads may reveal only equivocal evidence of posterior myocardial lesions.

Normal standards must be established before the abnormal can be recognized. Such standards have been determined for Leads I, II, and III[1-5] and for the normal unipolar limb and precordial leads.[6-14] A search of the available literature, however, reveals only a few articles in which the normal esophageal lead electrocardiogram is described.[17-21] Each of these descriptions has been based for the most part on relatively few normal subjects, and most were presented only for the purpose of comparison with a case or subject under discussion. These few reports are in themselves inadequate as bases for normal standards. The present study was undertaken to help fill this gap; it consists of an analysis of the esophageal lead electrocardiograms obtained in 40 normal subjects.

METHODS

Electrocardiograms were made on standard equipment, utilizing a small pear-shaped brass esophageal electrode as the exploring electrode and the central terminal of Wilson as the indifferent electrode. A comparative study was also made of brass and nickel-silver electrodes. The electrocardiograms were recorded at a paper speed of 25 mm. per second; all potentials were corrected to a standardization of 1 cm. equals 1 mv. The subjects were normal nurses, medical students, and house staff officers, together with a group of patients with normal hearts.

Records were made through a brass electrode which has been modified since the study was started. The electrodes now in use consist of 4 small pear-shaped brass tips, each measuring 3 by 5 mm., soldered to Litz No. 8817 wires. The wires are passed through a polyethylene catheter of 0.067 inches in outside diameter, and each is soldered to a separate terminal. The electrodes are permanently fixed 2.5 cm. apart. In this form, they may be swallowed and usually retained for as long as necessary. Most subjects have little difficulty in retaining the

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electrodes for an hour or more. After passage, the catheter may be gently gripped between the teeth by the subject in order to prevent movement; the plastic material is not harmed by this procedure.

Electrocardiograms were obtained in the following manner. The seated or recumbent subject swallowed the electrode to a distance of 50 to 55 cm. from the mouth and then lay quietly in order to allow esophageal peristalsis to subside.

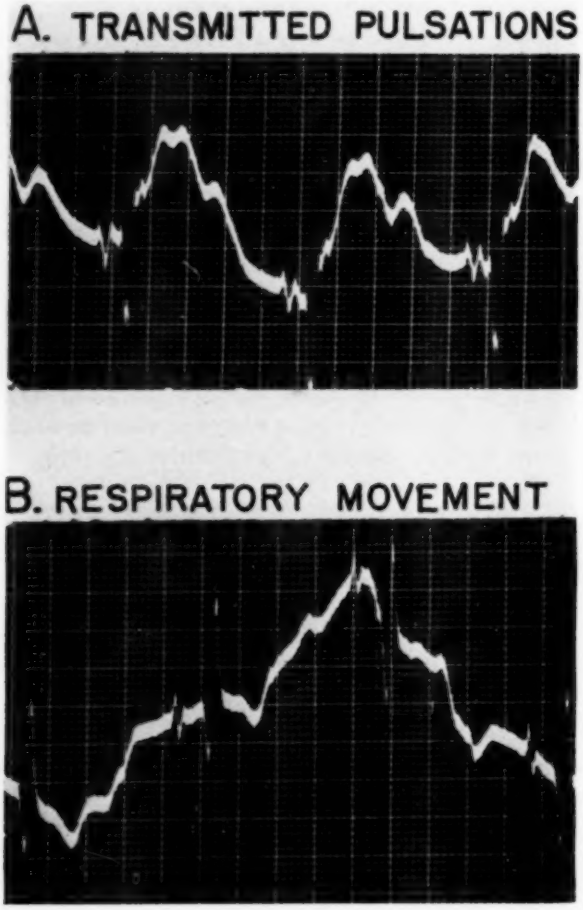

Fig. 1.—Artifacts encountered in esophageal lead electrocardiograms. *A* shows the effect of transmitted aortic pulsations. There is a definite distortion following each ventricular complex. This artifact is found most often at high atrial levels. *B* shows the characteristic undulation of the base line caused by respiratory movements. Comparison of both atrial and ventricular complexes at different parts of the record shows the pronounced distortion caused.

The longer distance (55 cm.) was necessary in tall subjects; 50 cm. or less was usually adequate in medium or short subjects. After an electrocardiogram was recorded at a given level, the catheter was withdrawn any desired distance, and another tracing was made at the new level. By use of the multiple-tip electrode, 2 to 4 successive or simultaneous leads might be studied without moving the

electrode. In this manner, the entire surface of the heart adjacent to the area of the esophagus from 50 to 55 cm. to 20 to 25 cm. from the mouth might be explored. The esophagus is directly posterior to the left atrium, and in the region near the diaphragm is adjacent to the caudal portion of the right atrium. It also lies near the posterior wall of the left ventricle. In its retroatrial course, the esophagus passes approximately directly behind most of the length of the interatrial septum.

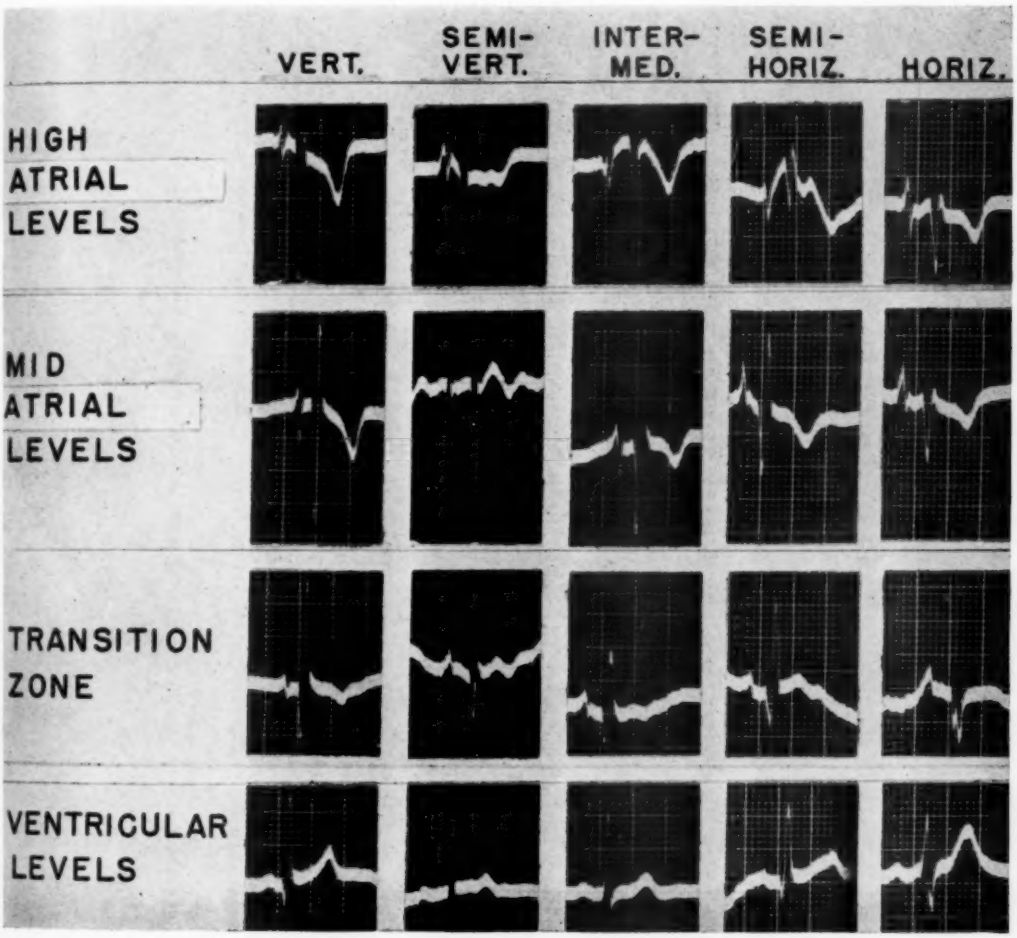

Fig. 2.—Representative electrocardiograms from each of the levels described in the text. Each of the 5 electrical positions of the heart is illustrated.

Artifacts.—Artifacts may distort esophageal electrocardiograms to such an extent that the record cannot be interpreted. The main causes of artifacts are respiratory movements and the proximity of the electrode to the aorta (Fig. 1). Esophageal peristalis may also distort the record, but it can be minimized if the subject lies quietly after passage of the electrode and if the electrode is pulled

TABLE I. ESOPHAGEAL LEAD DATA

LEVEL*	DURATION P†					POTENTIAL P_R‡					POTENTIAL P_a					VAT§				
	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.
Atrial																				
1	26	0.12	0.06	0.09	0.014	28	0.55	0.00	0.035	0.111	25	0.40	0.03	0.144	0.088	22	0.080	0.005	0.038	0.022
2	27	0.12	0.04	0.08	0.020	29	0.42	0.00	0.113	0.121	31	0.59	0.00	0.204	0.162	20	0.075	0.005	0.056	0.014
3	36	0.12	0.04	0.09	0.018	37	0.50	0.00	0.131	0.233	36	0.68	0.00	0.260	0.176	31	0.070	0.010	0.058	0.011
4	39	0.12	0.05	0.08	0.016	38	0.755	0.00	0.227	0.195	38	0.67	0.00	0.274	0.221	36	0.085	0.015	0.059	0.017
5	38	0.11	0.05	0.08	0.015	38	0.870	0.01	0.271	0.238	38	0.98	0.00	0.283	0.215	37	0.080	0.045	0.060	0.008
6	39	0.12	0.05	0.08	0.021	40	0.99	0.02	0.290	0.222	38	0.40	0.00	0.125	0.088	38	0.075	0.035	0.058	0.008
Transitional																				
7	38	0.12	0.06	0.09	0.019	37	0.73	0.04	0.237	0.150	36	0.18	0.00	0.059	0.051	36	0.070	0.005	0.052	0.011
8	39	0.12	0.05	0.09	0.017	40	0.41	0.01	0.124	0.077						40	0.065	0.015	0.044	0.011
Ventricular																				
9	36	0.12	0.06	0.09	0.017	38	0.39	0.01	0.109	0.071						38	0.060	0.015	0.040	0.010
10	37	0.12	0.06	0.09	0.018	39	0.22	0.04	0.104	0.072						39	0.055	0.005	0.039	0.010
11	35	0.12	0.04	0.09	0.021	36	0.14	0.02	0.082	0.032						38	0.055	0.015	0.039	0.009

*For purposes of making determinations at comparable levels in a large group of subjects, the transition zone was determined in each subject, and levels were studied at 2.5 cm. intervals in each direction away from the transition zone. Thus, the distance between each level given here is 2.5 cm.

†All durations in this and the succeeding tables are times in seconds.

‡All potentials given in this and the following tables are in millivolts.

§VAT refers to "ventricular activation time" and is synonymous with "time of onset of the intrinsic deflection."

TABLE II. ESOPHAGEAL LEAD DATA

LEVEL	DURATION Q					POTENTIAL Q					POTENTIAL R					POTENTIAL S				
	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.
Atrial																				
1	27	0.040	0.00	0.018	0.018	27	2.45	0.00	0.635	0.505	26	0.55	0.00	0.138	0.130	33	2.35	0.00	0.431	0.327
2	31	0.040	0.00	0.032	0.010	31	3.11	0.00	0.910	0.709	30	0.65	0.00	0.105	0.152	28	1.600	0.00	0.183	0.381
3	37	0.050	0.00	0.033	0.010	37	2.66	0.00	1.240	0.549	37	0.70	0.00	0.186	0.193	37	1.410	0.00	0.076	0.294
4	38	0.040	0.00	0.033	0.009	38	2.28	0.00	1.282	0.523	39	1.13	0.00	0.331	0.367	38	1.100	0.00	0.055	0.190
5	37	0.040	0.00	0.032	0.008	37	2.15	0.00	1.127	0.470	37	2.10	0.00	0.646	0.492	38	1.20	0.00	0.069	0.260
6	40	0.055	0.20	0.031	0.006	40	1.70	0.00	0.852	0.394	39	2.76	0.00	1.030	0.780	40	0.63	0.00	0.020	0.101
Transitional																				
7	38	0.060	0.00	0.028	0.009	38	1.61	0.00	0.611	0.382	38	3.87	0.00	1.110	0.842	39	0.97	0.00	0.095	0.237
8	40	0.030	0.00	0.012	0.010	40	1.31	0.00	0.210	0.276	40	2.98	0.00	1.128	0.762	40	1.20	0.00	0.175	0.201
Ventricular																				
9	37	0.030	0.00	0.009	0.008	37	0.43	0.00	0.117	0.108	38	3.02	0.078	1.176	0.714	39	1.77	0.00	0.218	0.409
10	38	0.025	0.00	0.008	0.007	38	0.36	0.00	0.096	0.097	40	3.13	0.082	1.255	0.730	40	1.46	0.00	0.157	0.312
11	36	0.015	0.00	0.006	0.005	36	0.30	0.00	0.074	0.084	38	3.10	0.110	1.257	0.707	39	0.89	0.00	0.155	0.247

TABLE III. ESOPHAGEAL LEAD DATA

LEVEL	S-T (+)					S-T (−)					T (+)					T (−)				
	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.	NO. POINTS	MAXIMUM	MINIMUM	MEAN	S. D.
Atrial																				
1	4	0.07	0.03	*	*	20	0.22	0.02	0.098	0.063						24	0.81	0.16	0.387	0.193
2	4	0.12	0.02			22	0.23	0.02	0.127	0.063	1	0.20				28	0.68	0.03	0.373	0.174
3	3	0.10	0.01			25	0.30	0.02	0.130	0.055	2	0.51	0.20			35	0.94	0.34	0.440	0.214
4	9	0.20	0.01			22	0.31	0.03	0.137	0.077	2	0.25	0.05			37	1.00	0.05	0.478	0.233
5	4	0.05	0.01			25	0.30	0.05	0.134	0.100	3	0.30	0.04			36	0.78	0.10	0.460	0.193
6	10	0.27	0.01	0.089	0.072	24	0.23	0.02	0.099	0.050	8	0.82	0.09			30	0.78	0.10	0.332	0.190
Transitional																				
7	11	0.16	0.04	0.070	0.043	14	0.32	0.01	0.120	0.078	10	0.95	0.04	0.231	0.264	24	0.50	0.06	0.237	0.132
8	16	0.14	0.01	0.067	0.034	7	0.25	0.05			32	0.82	0.03	0.287	0.170	7	0.20	0.01		
Ventricular																				
9	15	0.16	0.01	0.068	0.044	11	0.21	0.03	0.078	0.059	35	0.87	0.06	0.334	0.181	1	0.12			
10	23	0.20	0.01	0.077	0.050	6	0.06	0.02			38	1.10	0.11	0.360	0.195	1	0.05			
11	20	0.45	0.01	0.086	0.099	5	0.20	0.02			35	1.02	0.10	0.338	0.201					

*Mean and standard deviation of any given group have not been calculated unless the total in that group was 10 determinations or more.

slowly and gently when it is being withdrawn to higher positions. Respirations cause a cyclic drift of the base line (Fig. 1,*A*); this can be avoided if the subject holds his breath while the record is made. A satisfactory method is to have the subject inhale, then exhale to a mid-point of respiration, and hold his breath while the tracing is made. If the electrode is close to a tortuous or dilated aorta or to the arch of the aorta, transmitted pulsations may cause a distortion of the record after each beat (Fig. 1,*B*). This distortion can usually be avoided by raising the electrode a few millimeters.

RESULTS

Of the 40 subjects studied, 30 were male and 10 were female. As most of the subjects were young, the majority of records were made from hearts in a vertical or semivertical position: 17 were vertical, 14 semivertical, 4 intermediate, 3 semihorizontal, and 2 horizontal.

For the sake of convenience and clarity in interpretation, the esophageal electrocardiograms were divided into 3 main groups according to levels (distances in centimeters from the lips): ventricular, transitional, and atrial. Fig. 2 shows representative ventricular, transitional, and atrial electrocardiograms from 5 subjects. In addition, the atrial levels were divided into two subgroups, mid- and high atrial. Ventricular and atrial refer to those leads which primarily "tap" the potentials from each of those structures. There is a direct anatomic relationship between the structure studied and the finished tracing. Transitional refers to leads recorded in an area approximately directly posterior to the atrioventricular groove.

While the total sample studied was small, it was large enough to be statistically significant. Each level was analyzed in detail; the quantitative measurements of duration and potential of each component may be found in Tables I, II, and III.

Fig. 3 shows 4 simultaneous leads from a single subject to demonstrate from the various configurations (1) the pathway of the impulse from the sinoatrial node being in a cephalocaudal direction and (2) the relations of the upright and inverted components of the ventricular deflections in simultaneous leads.

Ventricular Levels.—The leads over the ventricular levels (usually 40 to 50 cm. from the mouth) were easily identified by their close resemblance to the apical precordial leads. The P wave was consistently upright and appeared as a gentle undulation that might have a slightly peaked appearance. The duration of the P wave was from 0.04 to 0.12 second; the maximum amplitude was 0.39 mv. This maximum potential was recorded at a level near the transition zone in a single patient. The next highest potential at a definite ventricular level as 0.22 mv.

There was frequently a small Q wave in the ventricular complex; the deepest Q waves appeared where the R waves were tallest. The maximum duration of the Q wave was 0.03 second from onset to nadir; the maximum amplitude found was 0.43 mv. Although a Q/R ratio of 0.373 was found at a high ventricular level in 1 subject (with Q_3 and Q_{AVF} in the usually accepted normal range), the ratio was much smaller in the other subjects; the second highest was 0.29.

The R waves were of greatest amplitude in the hearts in a vertical position, the maximum potential found being 3.13 mv. The S waves were often small or absent in the vertical hearts and were of greatest amplitude in the intermediate,

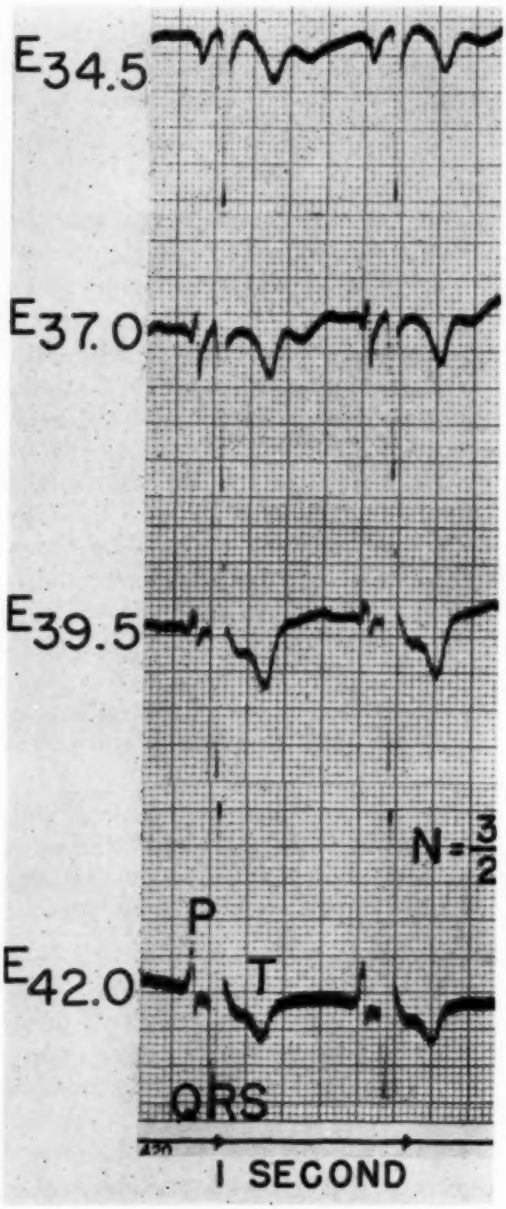

Fig. 3.—Simultaneous esophageal lead electrocardiograms extending from a high atrial level to the transition zone. The reciprocal relationships of the various parts of the ventricular complex as the electrode positions vary from ventricular to high atrial are clearly illustrated. From a consideration of the configuration of each P wave and the approximate time of onset of each atrial intrinsic deflection, it is seen that the normal sinus impulse originates near the high atrial levels and travels in a cephalocaudal direction.

semihorizontal, or horizontal hearts; in these positions the maximum was 1.77 mv. The R and S waves maintained fairly consistent potentials over the entire ventricular surface until the transition zone was reached; as described later, there were marked changes in this area.

As a rule, there was slight S-T elevation or depression. The T waves were upright in each subject, regardless of the electrical axis. The time of onset of the intrinsic deflection was always less than 0.06 second at this level and was usually remarkably consistent over the entire ventricular surface of a given heart as examined through the esophagus. (The maximum value of 0.06 second was found in only 1 subject at a level near the transition zone. Below that level, the longest time found was 0.055 second.)

Transition Zone.—This zone, the dividing line between the ventricular and atrial levels, hence located over the atrioventricular groove, usually occurs over a 2.5 cm. width; that is, it occupies 1 or 2 levels. In this series, it was found between 32.5 cm. and 45 cm. from the mouth; in 75 per cent of the subjects it was between 37.5 cm. and 42.5 cm. Evidence of the transition may appear first in either the ventricular or the atrial complexes. There may be a change in configuration of the P wave with a greater amplitude and sharper peak; often a biphasic P wave appears. A definite intrinsic deflection may be present in the P wave at this level. The Q wave may be deeper and broader, and the R wave often smaller than over the ventricular levels. The T waves may be flat or inverted. The S wave is frequently absent in this zone; the sudden disappearance of a previously present S wave may mark the transition. At other times, the R wave may be temporarily absent; in these instances the ventricular complex consists solely of a QS wave.

The duration of the P wave ranged from 0.05 to 0.12 second. The maximum amplitude of the upright portion of the P wave at this level was 0.73 mv.; that of the inverted part of the P was 0.18 mv. The maximum duration of Q from onset to nadir was 0.06 second. The maximum Q wave was 1.6 mv., the tallest R was 3.87 mv., and the deepest S was 1.20 mv. The S-T segment might be elevated or depressed. A part of the rather extreme elevation or depression found at these levels and in others (particularly the atrial) may be related to a superimposed T_a segment or wave. The T waves might be either upright or inverted; there was no correlation between the configuration of the QRS complex and the positivity or negativity of the T wave. The time of onset of the ventricular intrinsic deflection was prolonged as compared with that over the ventricular level; the longest time found was 0.07 second.

Atrial Levels.—The atrial levels extend 10 to 15 cm. cephalad from the transition zone. At the lowest levels, potentials were recorded from both right and left atria; at mid- and high atrial levels, left atrial potentials were predominant. There were characteristic changes in the P wave. Over these levels, the P waves were always biphasic or triphasic and had a definite intrinsic deflection; they corresponded closely in configuration to the atrial complexes seen in direct atrial leads in dogs.[25] The P waves were always completely inverted at the supraatrial levels. Over the highest atrial levels a small negative deflection might

occur; this might be followed by a tiny upright component. The main deflection was a deep negative wave which was always present. At progressively lower levels the upright component became taller. The initial negative wave might persist, but it eventually disappeared before the transition zone was reached. The deep negative wave which followed the positive component was of variable amplitude but disappeared at the lower atrial levels. The P waves at the subatrial levels were always upright. The duration of the P wave varied from 0.04 to 0.12 second. The amplitude of both the positive and negative deflections of the P wave varied greatly; the tallest was 0.99 mv., and the deepest was 0.98 mv.

The time of onset of the atrial intrinsic deflection was later at the lower than at the higher levels. In several simultaneous records of levels at the caudal and cephalic ends of the atria, the difference in time of onset of the intrinsic deflections from the two extremities was always less than 0.02 second.

There was a definite deviation in the base line immediately after the P wave and before the QRS in many of the atrial leads, especially the mid-atrial; this often caused a marked elevation or depression of the first portion of the ventricular complex. The elevation or depression usually took a direction opposite to the main deflection of the P wave. These changes apparently represented an effect of the T_a segment.

The ventricular complex had a deep wide Q wave, which increased in both amplitude and duration over the higher atrial levels. The longest Q was 0.055 second from onset to nadir in 1 subject. Here the wave was actually a QS. The next longest Q was 0.05 second. The deepest Q was 3.1 mv. in high atrial leads. The R wave was often tall over the lower atrial levels, but it became progressively shorter at higher levels. The tallest R was 2.76 mv. The Q wave was often replaced by a tiny R wave in the highest atrial levels; this R was followed by a deep S wave. The deepest S wave was 2.35 mv. A minute R′ might appear at the higher atrial levels. The time of onset of the intrinsic deflection was progressively later over the higher atrial levels and reached a maximum of 0.085 second. In those instances in which there was a tiny R wave and no R′, the time of onset of the intrinsic deflection was very short; it might be as little as 0.005 second.

The S-T segments were elevated or depressed. As the elevation or depression was oppositely directed to the P wave, this phenomenon may be related to the T_a segment. A characteristic feature of the atrial levels was the constantly inverted T waves, the inversion being less near the transition zone than at the cephalic end of the atrial levels.

The supra-atrial levels uniformly tended to resemble Lead aV_R in configuration, duration, and potential of each component.

Comparison of Brass and Nickel-Silver Electrodes.—The possibility was suggested that polarization effects from the brass electrodes used in this study altered the results obtained. It was suggested also that nickel-silver be used instead of brass. In order to check our findings, 2 electrodes were made. These were identical except for the electrode tip; one was made of brass, the other of nickel-silver. Records were made from semidirect mediastinal leads from identical positions in an identical manner in each of 4 dogs. As shown in Fig. 4,

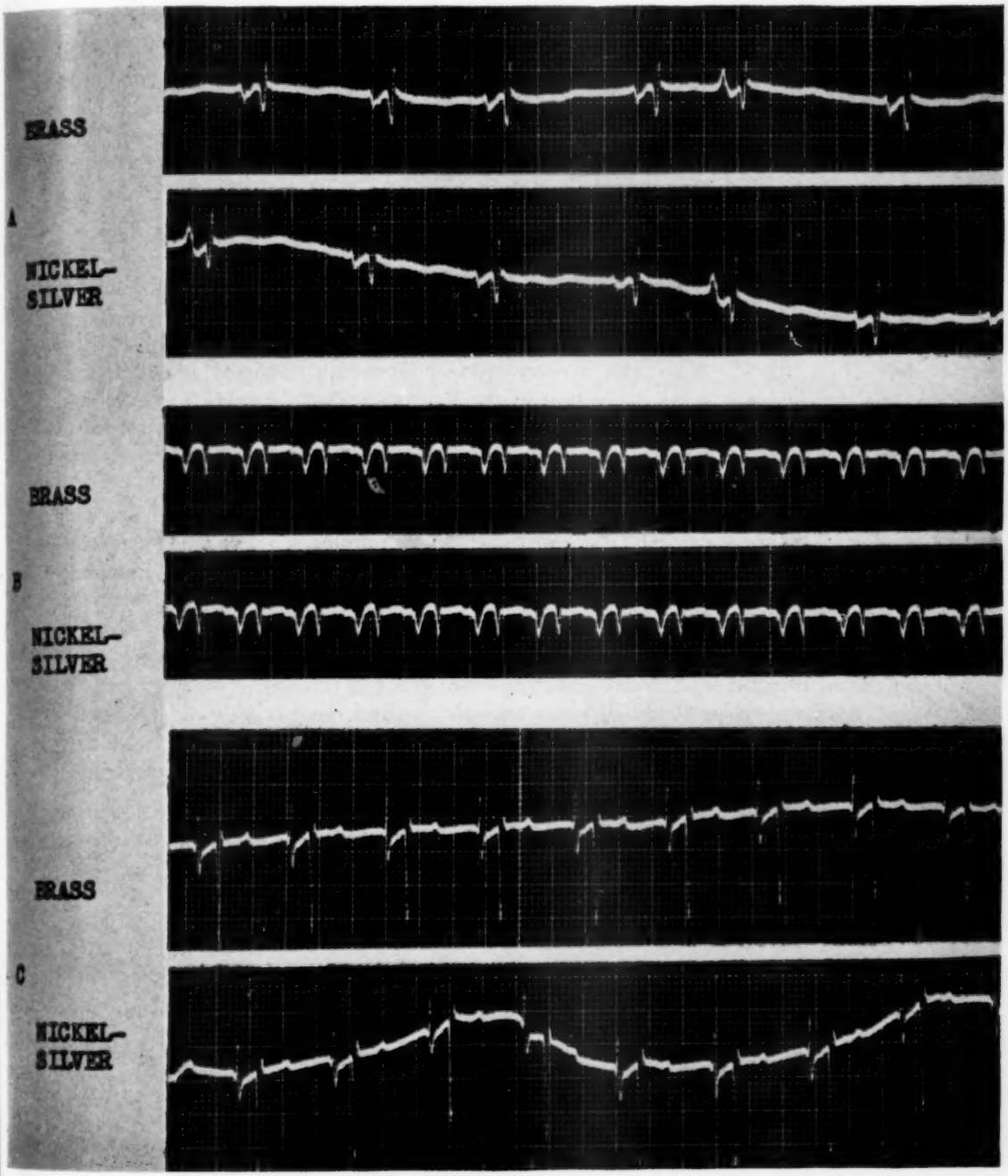

Fig. 4.—Representative semidirect mediastinal lead electrocardiograms to show a comparison of brass and nickel-silver electrodes. *A* is from the superior vena cava, *B* from the superior vena cava, and *C* from the inferior vena cava lateral to the right auricle. No appreciable polarization effect is present. Minute variations within paired records are due to tiny differences in location of the electrodes in a given animal.

the tracings obtained were closely similar or identical. There was no P-Q, RS-T, or T-P shift suggestive of a galvanic current of significant degree. Minute differences present in the electrocardiograms obtained from each electrode could be accounted for by slight unavoidable differences in the position of each electrode. It is concluded, therefore, that for practical purposes brass appears suitable for use in esophageal lead electrodes. Whatever changes may be present from polarization effects have no clinical significance.

SUMMARY

The esophageal lead electrocardiogram has been analyzed in 40 normal subjects.

As a rule, the records at ventricular levels closely resembled those from left chest leads. Near the atrioventricular groove (transition zone) and at atrial levels, an intrinsic deflection in the P wave, a deep broad Q, progressively smaller R and deeper S, and inverted T waves appeared. Immediately behind the atria, the P wave was of shorter duration, of greater complexity in configuration, and of greater voltage in all its components than elsewhere. T_a (auricular repolarization) waves were frequently present in leads from this region. At these same levels, the ventricular complexes approached the configuration seen in Lead aV_R, and at supra-atrial levels were almost identical. The P wave became inverted in the supra-atrial leads and resembled that seen in aV_R.

The maximum and minimum duration and amplitude of each component of the esophageal lead electrocardiogram are given in tabular form.

A comparative study of brass and nickel-silver esophageal lead electrodes shows that there are at most minute differences in the records obtained with each type. Brass electrodes appear suitable for use as esophageal lead electrodes.

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THE ESOPHAGEAL ELECTROCARDIOGRAM IN THE STUDY OF ATRIAL ACTIVITY AND CARDIAC ARRHYTHMIAS

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IN CLINICAL electrocardiography the atrial complex is often so small in conventional leads that it does not permit of careful study. Inconspicuousness of the P wave may render impossible the exact diagnosis of cardiac arrhythmias. It is perhaps no exaggeration to say that a precise knowledge of atrial activity is the key to the diagnosis of many arrhythmias. In efforts to improve the recording of atrial activity, various exploratory methods have been advocated. These include certain precordial and esophageal leads.

The exploratory precordial leads comprise many combinations of placement of the chest and distant electrodes, the former usually located at, or to the right of, the sternum in more or less anatomic relation to the right atrium.[1-16] While such leads frequently reveal atrial deflections better than limb leads, cases of arrhythmias are often seen in which the mechanism cannot be elucidated even with these methods. In such cases recourse to esophageal electrocardiography may be advisable.

The earliest reports on clinical esophageal electrocardiography were scanty and empirical.[17-21] Brown, in 1936, established it as a sound and rational procedure.[22,23] His classical studies proved the validity of regarding the rapid intrinsicoid deflection of the P wave at certain esophageal levels as being truly comparable with the intrinsic deflection obtainable directly from the left atrium. As a result of using the polarity prevailing at the time, however, all his illustrations are reversed by present standards. A recent study confirmed the belief that true intrinsicoid deflections are obtainable by esophageal leads, and that these leads are the only true semidirect ones for the atrial muscle in man.[24] There have been several important contributions to the study of esophageal electrocardiography, but most of them deal with the form of the ventricular complex[25-29] or with myocardial infarction.[30-34] No study of a large series of arrhythmias by this method has been reported since Brown's publications.

It is the purpose of this paper to describe the appearance of the esophageal electrocardiogram in a variety of arrhythmias and to evaluate the aid which this method may offer toward their diagnosis.

METHOD

Both homemade and commercial esophageal electrodes were used. Except in two cases, the tube was passed through the nose. Records were made on

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several types of electrocardiographs, most of them on Cambridge string galvanometers. Esophageal electrocardiograms were made through a Wilson unipolar connection. Records were recorded at various levels between 22 and 57 cm. from the anterior nares or teeth. In the accompanying illustrations these levels are indicated by the subscripts to the letter "E." The optimal levels for recording atrial activity are generally designated as E_A. Standardization was usually normal (1 mv. = 1 cm.), and all measurements of amplitude were corrected when necessary so that they could be expressed in millivolts. Standard limb leads were made in all cases, and in arrhythmias exploratory chest leads were made as well. These were chiefly CF and CR leads from the third and fourth interspaces at the right sternal border and, occasionally, xiphoid-manubrium leads.

CLINICAL MATERIAL

Altogether 111 esophageal electrocardiograms were made on ninety-eight subjects. The latter were chiefly patients with heart disease due to arteriosclerosis, hypertension, or rheumatic fever. Several subjects had no heart disease. The rhythmic mechanisms were:

Regular sinus rhythm	36
Sinus bradycardia	2
Sinus tachycardia	3
Sinus arrhythmia, marked	1
Sinus arrests	2
Atrioventricular rhythms	
Nodal rhythm	1
Interference dissociation	3
Atrioventricular block	
Incomplete (dropped beats)	5
Complete	6
Wolff-Parkinson-White conduction	2
Premature systoles	
Atrial	7
Nodal	1
His bundle	1
Ventricular	11
Paroxysmal tachycardia	
Sinus, with atrioventricular block	1
Atrial	2
Atrial, with atrioventricular block	6
Supraventricular	1
Nodal	1
His bundle	1
Atrial flutter	9
Atrial fibrillation	12

RESULTS

Form of the Normal Atrial Complex.—At ventricular levels, usually 50 cm. or more from the nares, the esophageal P wave resembled that in standard limb leads. It was always positive, rarely higher than 0.3 mv., and never showed an

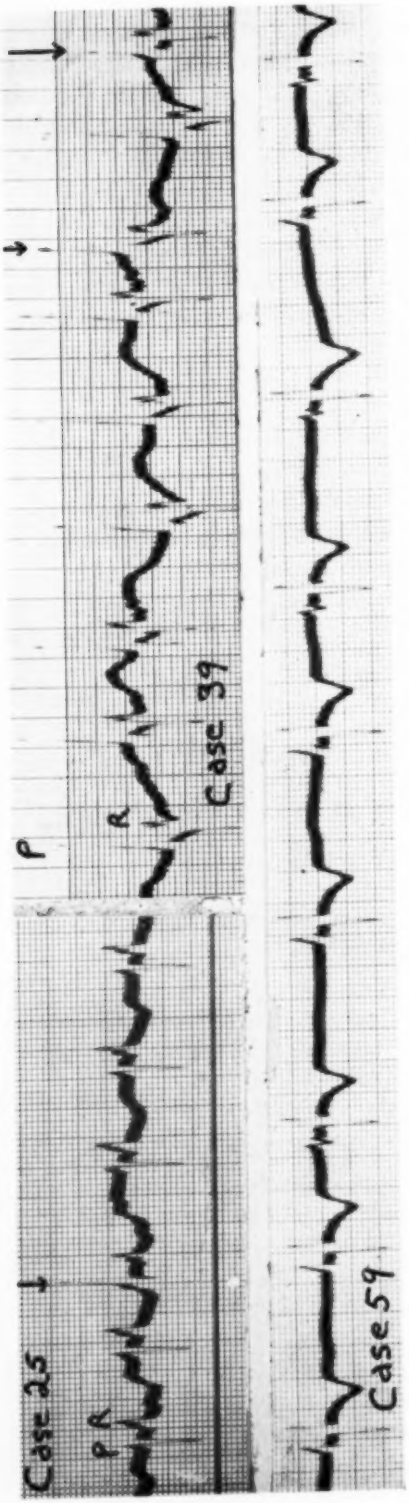

Fig. 1.—E_A: regular sinus rhythm and atrial premature systoles. Note the similarity of the sixth and seventh P waves in Case 59.

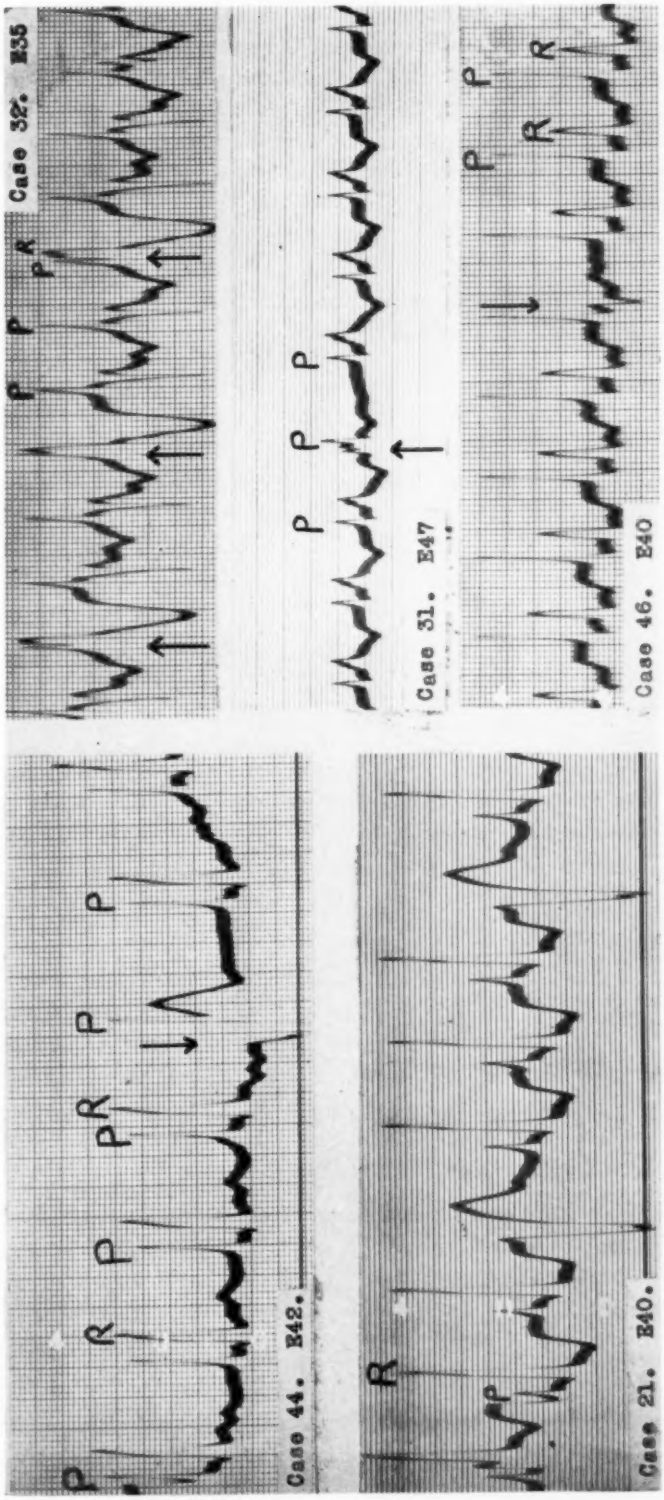

Fig. 2.—Regular sinus rhythm and ventricular premature systoles, showing varying degrees of prematurity. In Case 21 the P wave causes a notch in the S wave of the extrasystole.

intrinsic deflection. As the electrode tip was moved to higher levels, the amplitude of the P wave increased and its component parts became sharper. At atrial levels, usually between 30 and 45 cm., a distinctive form became evident. This consisted of a rise in potential to a peak much higher than that in conventional or exploratory leads, followed by a rapid excursion in a negative direction (the intrinsicoid deflection) and then a slower return to the base line. As the tip was moved still higher, the P wave gradually became smaller, broader, and more predominantly negative as in aV_R. Typical normal P waves are seen in Figs. 1 and 2. The form of the P wave was constant regardless of the rate of the sinus pacemaker except in a case of marked sinus arrhythmia in which there was considerable variation in the shape and size of the P wave.

TABLE I. AMPLITUDE OF INTRINSIC DEFLECTION OF P WAVE AT OPTIMAL ATRIAL ESOPHAGEAL LEVELS (E_A)

AMPLITUDE (MV.)	NO. CASES	AMPLITUDE (MV.)	NO. CASES
0.05–0.12	2	0.91–1.1	14
0.15–0.20	2	1.2–1.4	10
0.21–0.30	2	1.5–1.7	9
0.40–0.50	11	1.8–2.1	4
0.51–0.70	12	2.2–2.4	2
0.71–0.90	14	2.5	2

The amplitude of the intrinsicoid deflection of the P wave varied from 0.05 to 2.5 mv. in eighty-four cases. It exceeded 0.3 mv. in seventy-eight of these, and in over one-half of the cases, it was greater than 0.7 mv. (Table 1). The width of the P waves varied from 0.06 to 0.11 second, and occasionally a small negative wave marked the beginning of atrial activity. The time of onset of the intrinsicoid deflection was 0.04 to 0.06 second after the beginning of electrical activity.

T_a Wave.—Atrial T waves were often seen during incomplete as well as complete heart block (Fig. 3). These waves were up to 0.4 mv. in size, although usually 0.1 to 0.3 mv., and were oppositely directed to the main atrial deflections. The intervals between the beginning of P and the end of T_a varied from 0.22 to 0.50 second. Variations in the duration of the P-T_a intervals were present at different atrial esophageal levels in the same cases, and there appeared to be no correlation with the length of the atrial cycles.

Esophageal P-R intervals tended to be distinctly shorter than those in limb leads or chest leads. The difference was most often 0.02 to 0.04 second, and in only two cases was the shortest P-R interval in a limb lead the same as in an atrial esophageal lead. The difference was greater in the patients with abnormally long atrioventricular conduction time, the maximal difference being 0.06 second.

Sinus Arrests.—The dropped-out P waves were very conspicuous by their absence in both cases. An example is shown in Fig. 4.

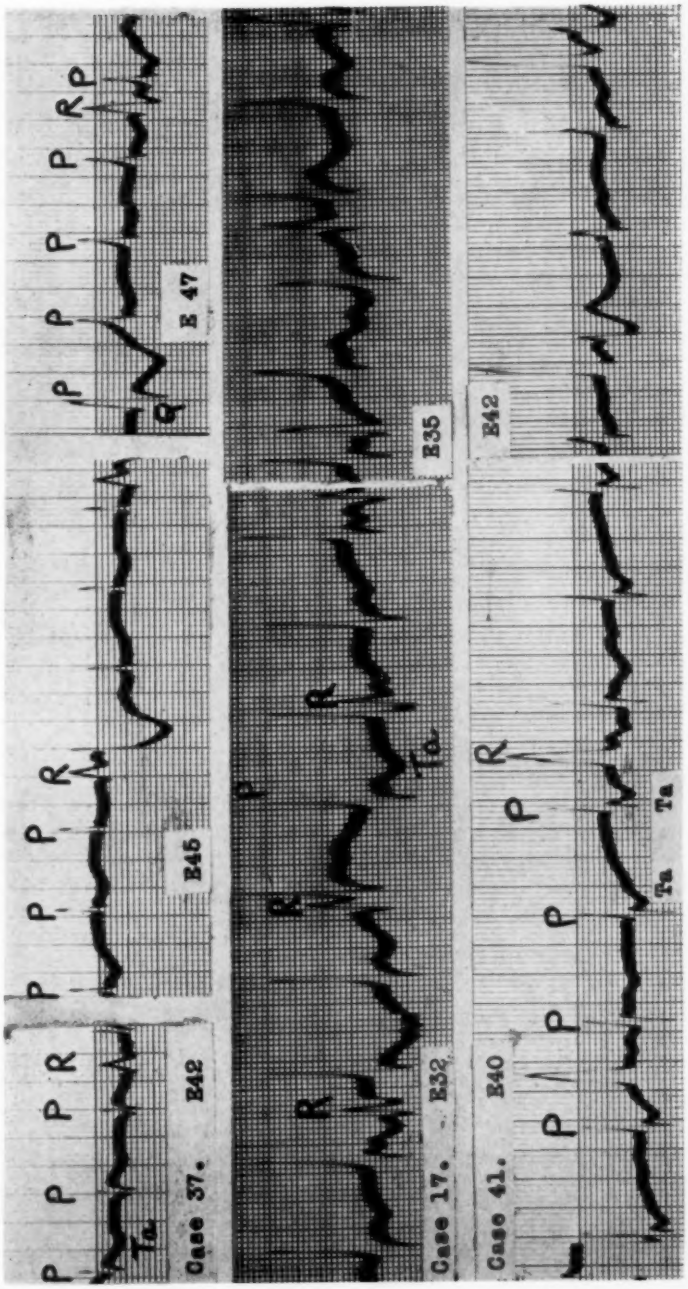

Fig. 3.—Complete heart block. T_a waves are easily seen except when they fall during inscription of ventricular waves.

Atrioventricular Rhythms.—

Nodal rhythm: Transient upper nodal rhythm was present in one case and showed P waves smaller than those arising from the sinus node with a P-R interval of 0.08 second. The record was too poor for reproduction.

Interference dissociation: In all three cases, the striking feature was the constancy of form of P waves regardless of whether they preceded, coincided with, or followed ventricular complexes. In one case this arrhythmia took a very interesting form (Case 61, Figs. 4 and 5).

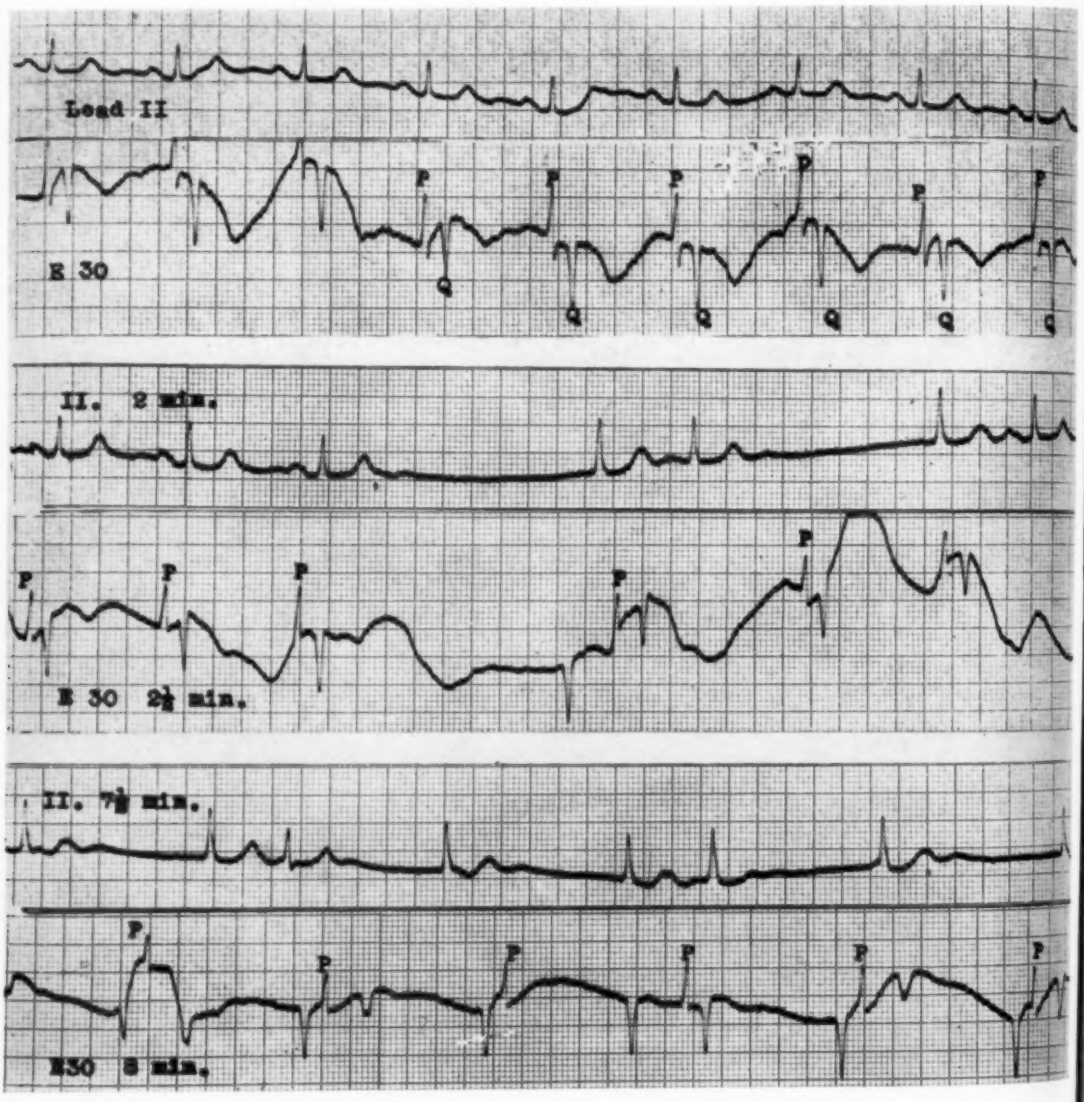

Fig. 4 (Case 61).—Sinus arrests and nodal escapes following acetyl strophanthidin (see text).

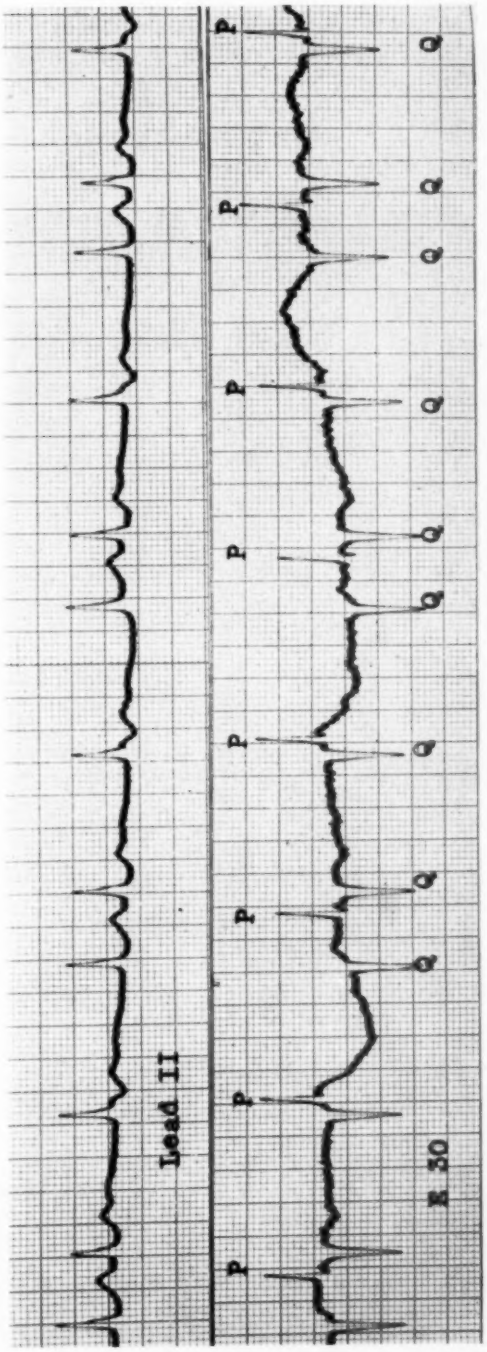

Fig. 5 (Case 61).—Complex arrhythmia. Lead II is mounted above E_{30} as though simultaneously recorded (see text).

Atrioventricular Block.—The outstanding feature of esophageal electrocardiograms in this group of eleven cases was the clear-cut disclosure of atrial T waves, even in patients with occasional dropped beats. In the latter, T_a waves became evident when the P-R interval lengthened, even before ventricular complexes dropped out (Fig. 16).

Wolff-Parkinson-White Conduction.—Both patients were examined during sinus rhythm and exhibited the same features. The ventricular complex was

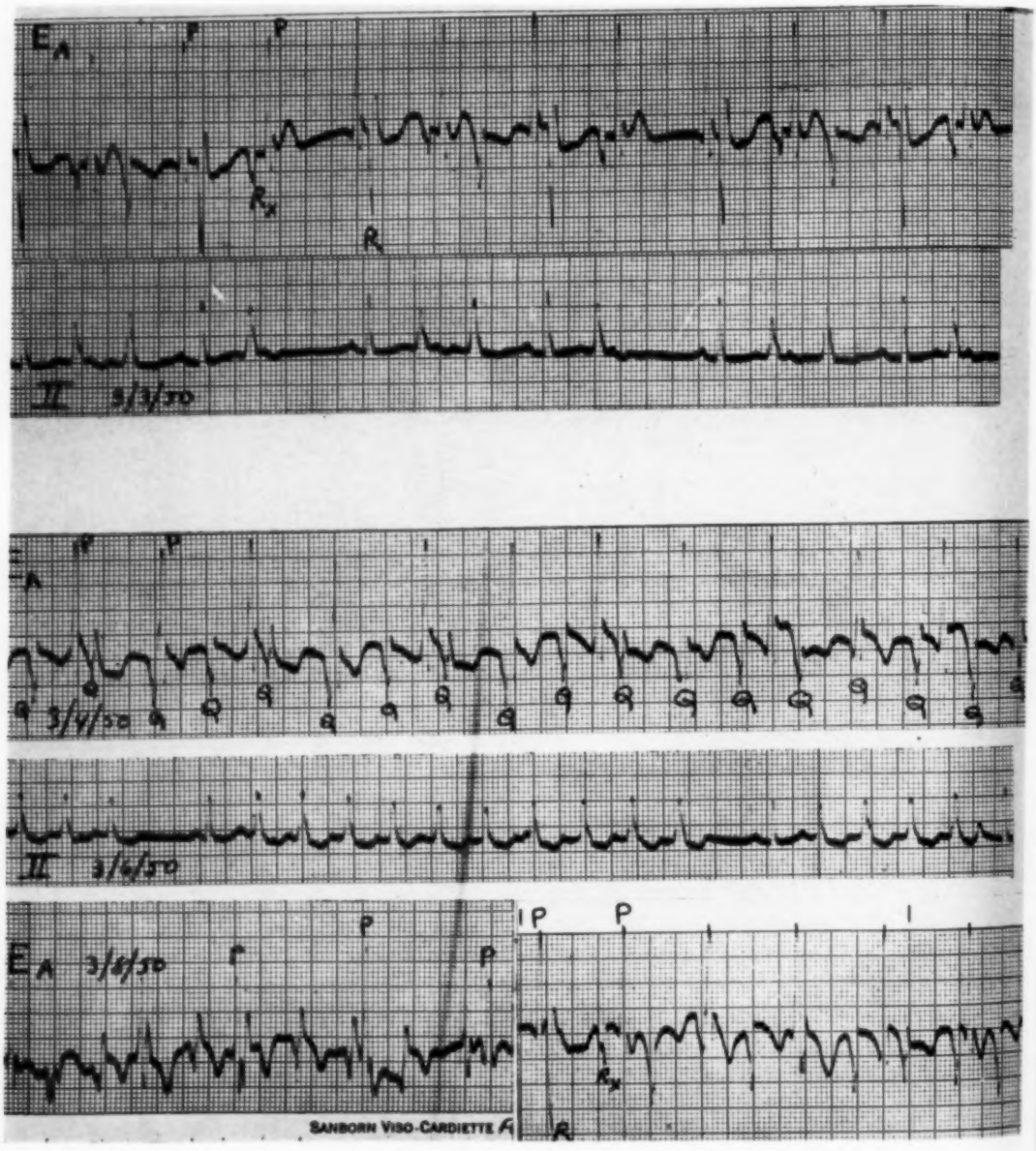

Fig. 6 (Case 86).—His bundle premature systoles (upper two rows) and His bundle tachycardia (lower three rows) (see text).

moderately aberrant and appeared to begin before the P wave had ended, making the measurement of the P-R interval at atrial esophageal levels uncertain.

Premature Systoles.—

Atrial: The ectopic complexes were strikingly different in form and amplitude from the normal complexes. In over one-half they were positive at atrial levels and taller than the normal P waves. In three cases postextrasystolic beats arose from the same ectopic focus as the premature beats (Fig. 1).

Nodal: Upper nodal premature beats occurred in one case and showed the same features as in the case of nodal rhythm.

His bundle: Esophageal records showed only slight aberration of ventricular complexes and no interference with the sinus activity (Fig. 6).

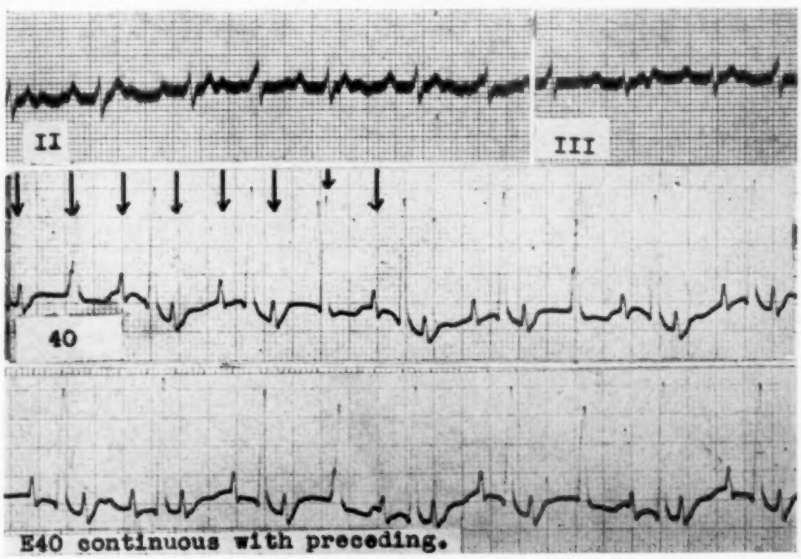

Fig. 7 (Case 7).—Atrial tachycardia with varying atrioventricular block; atrial rate 167, ventricular rate 93. Atrial premature beats present for four days preceding paroxysm.

Ventricular: In all eleven cases the postextrasystolic P waves stood out sharply (Fig. 2).

Paroxysmal Tachycardia.—

Sinus: In one case the atrial rate was 122 and the ventricular rate 61 due to 2:1 block at the height of the paroxysm. P waves were slightly different in form and size from those during normal rhythm, and there were small variations in atrial cycle length during the paroxysm.

Atrial: Two patients without atrioventricular block showed aberrant P waves at atrial levels, but it was not possible to compare these with the P waves during normal rhythm. In addition to slurring, both patients had negative P waves at low esophageal levels and positive P waves at high levels. Six cases were associated with atrioventricular block varying in grade from less

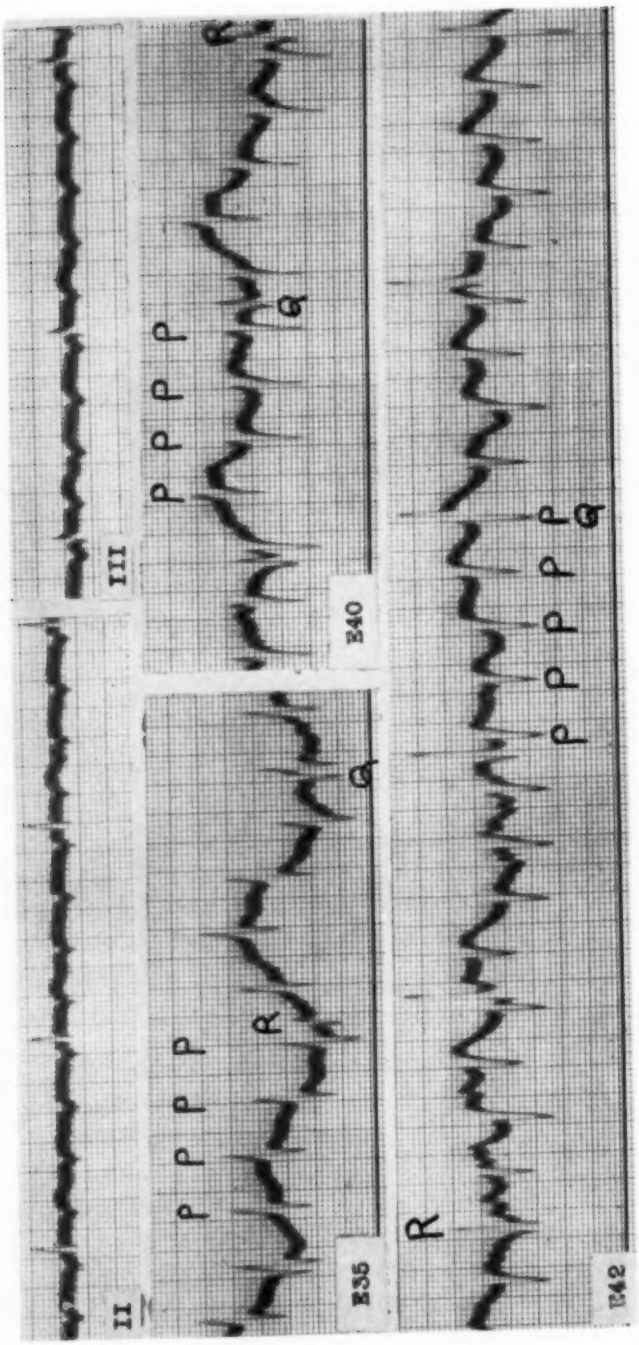

Fig. 8 (Case 56).—Atrial tachycardia with high-grade atrioventricular block: atrial rate 158, ventricular rate 30 to 42 (see text).

than 2:1 to 6:1 (Figs. 7 and 8). Negative P waves at infra-atrial levels and positive P waves at supra-atrial levels were present in two of these cases.

Supraventricular: In one case the esophageal P-R interval was 0.10 second, and conventional P-R intervals were 0.12 to 0.13 second. In two other cases of supraventricular tachycardia the paroxysms were abruptly terminated during the passage of the esophageal electrode.

Nodal: One patient showed small but sharp P waves with a P-R interval of 0.10 second at atrial levels and P-R intervals of the same duration in right chest leads.

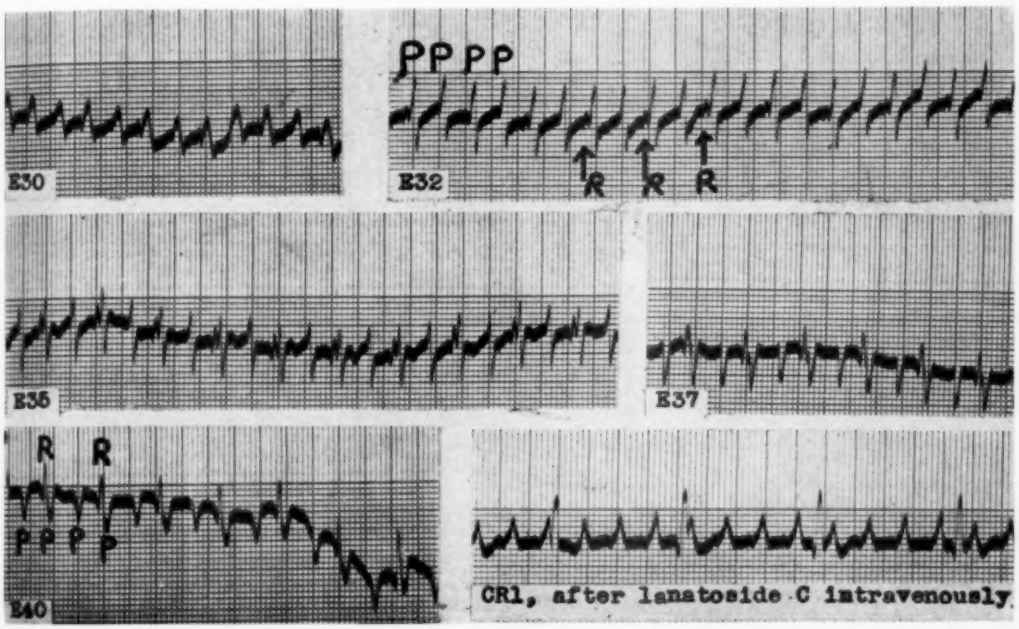

Fig. 9 (Case 35).—Rheumatic heart disease; characteristic appearance of atrial flutter. Note the relative size of P and R waves in E_{30}, E_{32}, and E_{35}.

His bundle: The paroxysms were preceded and followed by isolated premature systoles from the same ectopic focus. During paroxysms the independence of the sinus node was evident (Fig. 6).

Atrial Flutter.—Thirteen esophageal electrocardiograms were made on the nine cases. Atrial complexes were clearly shown in all, and all exhibited ascending base lines in the P-R intervals. In three cases where esophageal records were obtained during normal rhythm, definite differences in form of P waves from those during flutter were seen. In all the cases of flutter intrinsic deflections were present in atrial complexes (Figs. 9 to 15). In three cases P waves were predominantly negative at infra-atrial levels and positive at supra-atrial levels. In one case when only two atrial levels were recorded, the ascending base lines were not apparent, but on subsequent examinations they were easily seen (Case 15, Figs. 11 and 12).

Atrial Fibrillation.—Ten of the twelve patients showed only small, rapid, grossly irregular oscillations representing atrial activity. In these cases atrial waves in right chest leads were at least as pronounced as those in esophageal leads. In two cases large atrial waves and intrinsic deflections were irregularly present in E_A. One of these (Case 87, Figs. 14 and 15) had other features of interest.

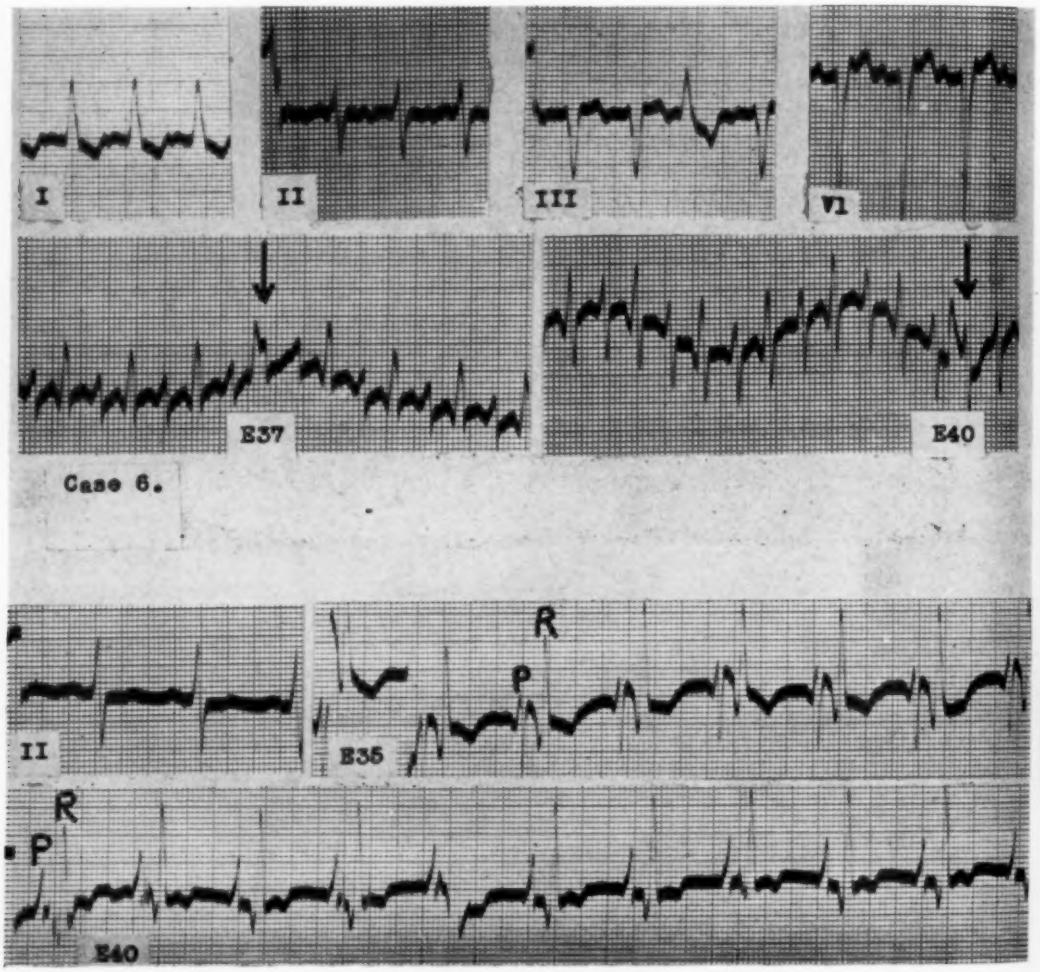

Fig. 10 (Case 6).—Concealed atrial flutter (see text). Lower two rows, same day after rapid digitalization.

DISCUSSION

Form of the Atrial Complex.—The findings in the present series are the same as those previously reported and serve to emphasize the remarkable constancy of the appearance of the P wave in the esophageal electrocardiogram.[22,28,31,35-38] The small negative wave sometimes seen at the onset of atrial activity is thought

to represent the initial activity of the sinus node itself. At optimal atrial levels the electrode tip is less than 1 cm. from the left atrium and about 5 cm. from the right. Hence, the conclusion is warranted that records at these levels represent left atrial events.[37]

The strong similarity between P waves recorded in E_A and those from within the right atrium has been repeatedly noted.[39-42] In the unusual cases where septal defects permitted electrocardiograms to be made from within the left atrium, these were practically the same as those from the right atrial cavity or E_A.[43,44] Direct electrocardiograms from the atrial surfaces in exposed human hearts are also indistinguishable from the above.[45] These observations corroborate the view that atrial activation is radial, from a single point.[1] The atria act electrically like a simple sheet of muscle.[46]

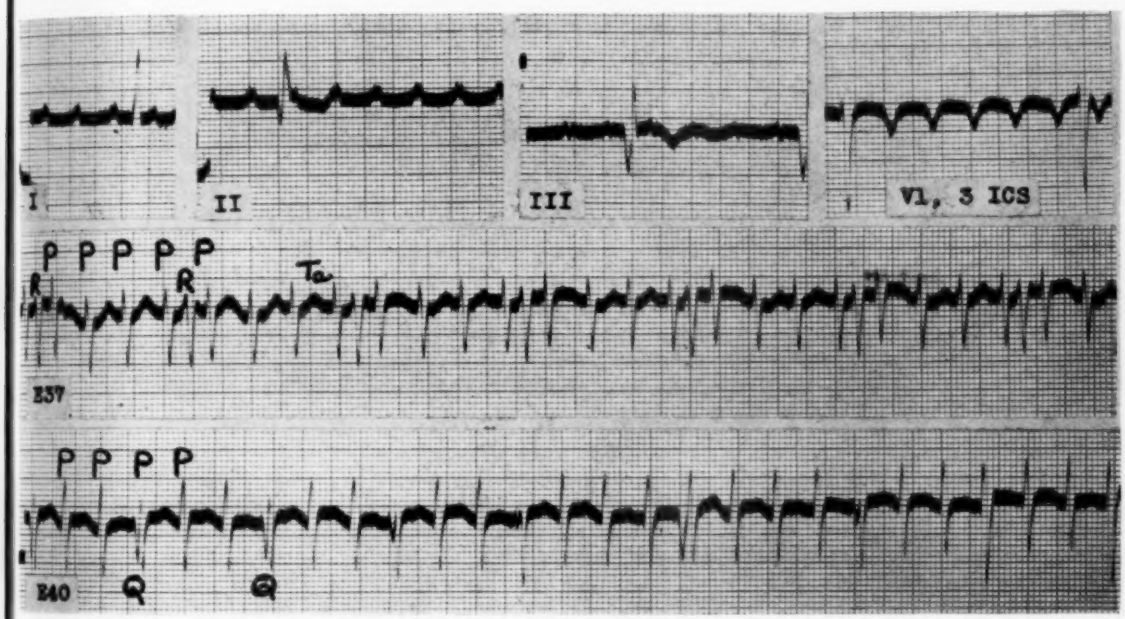

Fig. 11 (Case 15).—Sept. 13, 1947. Atrial flutter (see text).

The amplitude of the P waves in E_A is almost always far greater than in any other lead, and the sharpness of its components renders its recognition simple. Nevertheless, in two of our patients the P waves in E_A were much smaller than in right chest leads. Case 33, a patient with rheumatic and thyrotoxic heart disease, had minute P waves in all leads except one from the third right interspace at the sternal border (CF). This showed P waves of 0.3 mv., whereas the best P waves in E_A measured only 0.05 mv. Case 34, a patient with arteriosclerotic heart disease, had P waves measuring 0.65 mv. in a unipolar lead from the third right rib at the sternal border, but the P waves in E_A were only 0.12 mv. The explanation of these small P waves is not clear. In neither patient was there unusual atrial enlargement, nor was it probable that there was enough destruction of atrial tissue to account for the loss of potential.

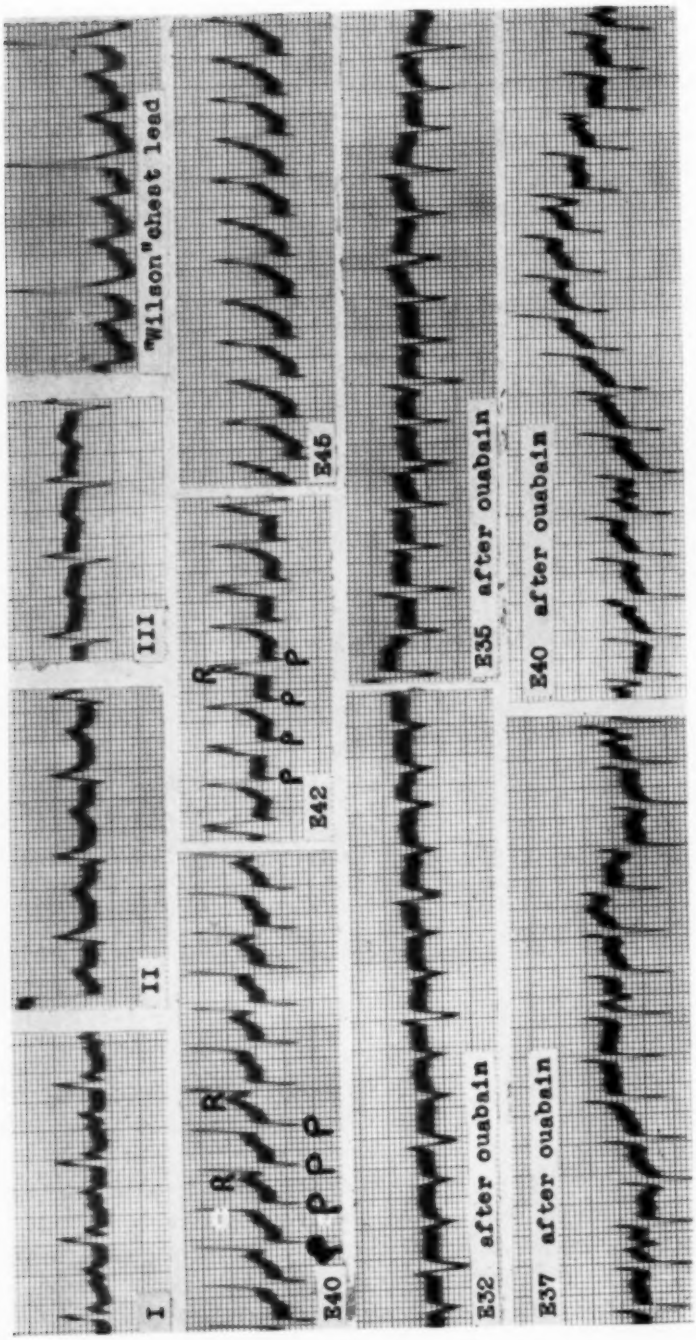

Fig. 12 (Case 15).—June 25, 1948. Atrial flutter (see text).

The range of width of the esophageal P waves in the present series (0.06 to 0.11 second) was greater than in other reported series.[22,35,38] Whether the width of the P waves, their amplitude, or the time of onset of intrinsic deflections is related to atrial enlargement could not be determined in the present study. This should be a subject for future investigation.

The end deflection or T_a wave of the atrial complex is rarely recognized in conventional records, though Sprague and White[47] found measurable T_a waves in eighteen of thirty-seven cases of heart block. The clinical importance of the T_a wave is not great. Certain instances of RS-T depression[22,48] and deformity

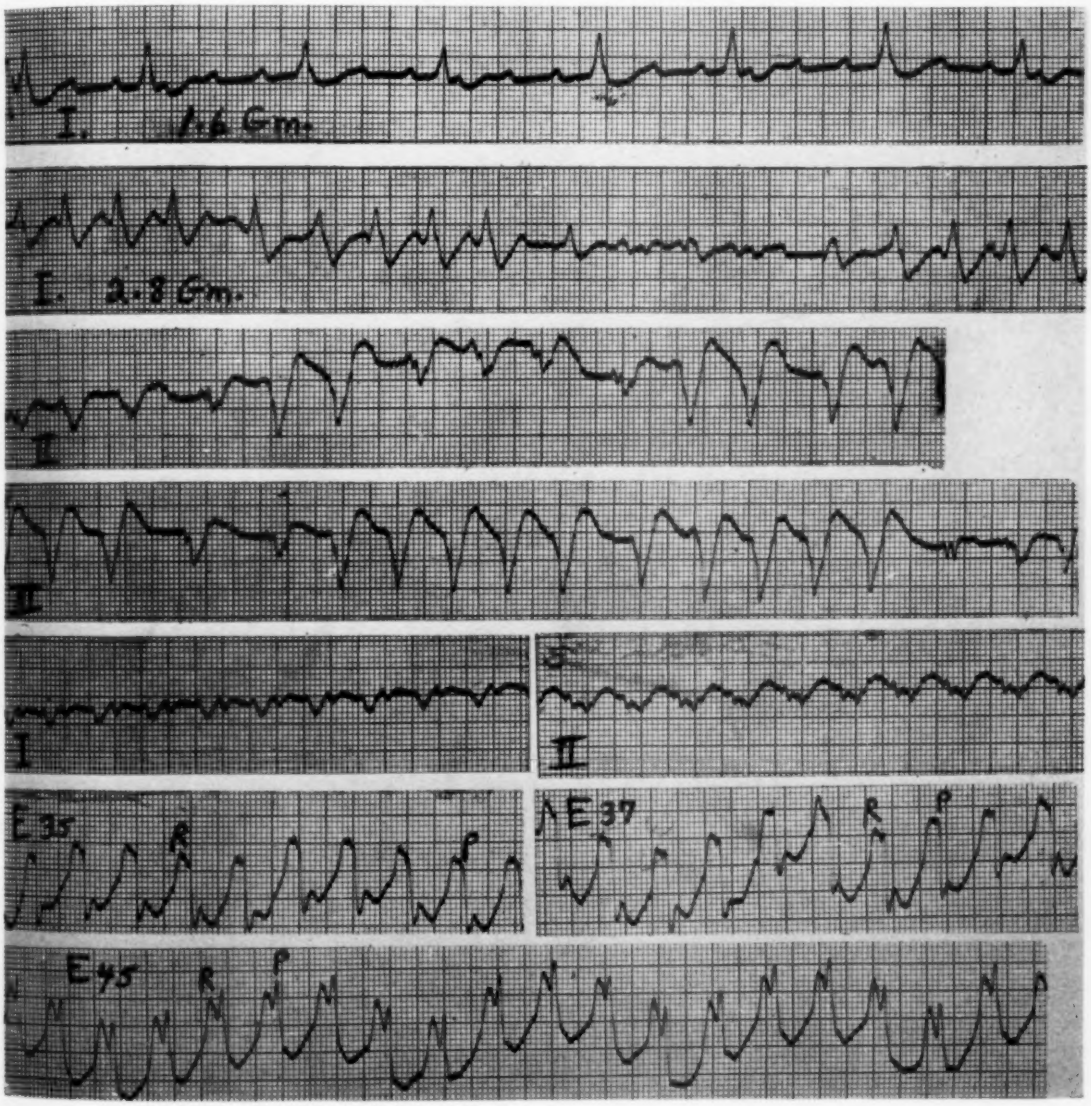

Fig. 13 (Case 15).—Jan. 18, 1950. Atrial flutter; 1:1 conduction and ventricular aberration after large doses of quinidine.

of the QRS complex[49] have been attributed to prominent or anomalous T_a waves. They have also been implicated as possible causes for displacement of the P-Q segment in limb leads,[50-55] suggestive of atrial hypertrophy or infarction. The esophageal electrocardiogram is well suited to such studies.

The short duration of the P-R interval in E_A as compared with other leads has been noted in comparisons with simultaneously recorded tracings from the right chest[56] and from the right atrial cavity.[42] The intrinsic deflection appears later in the left atrium than in the right.[42-45] On the basis of an unusually large

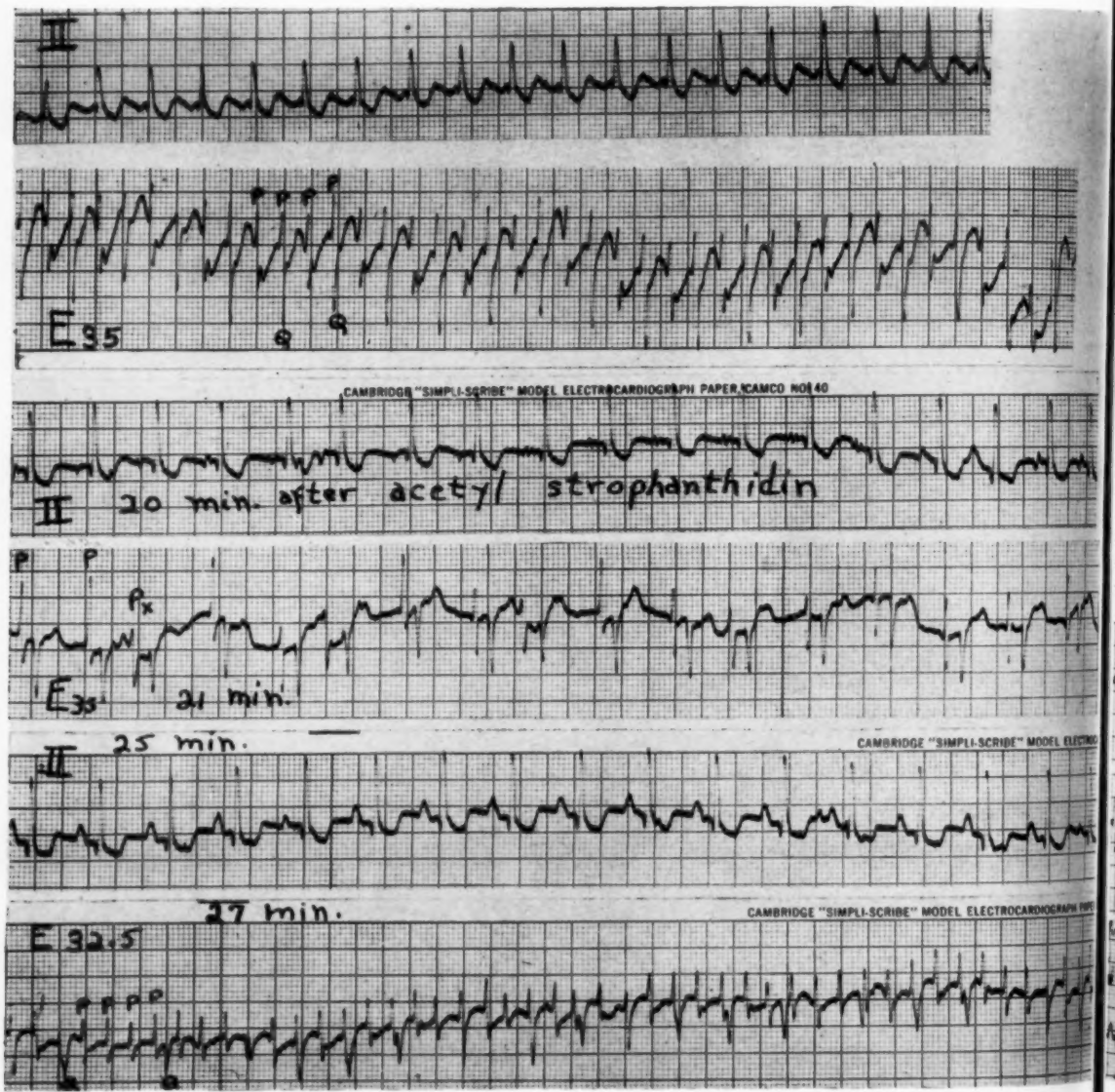

Fig. 14 (Case 87).—Atrial flutter converted transiently to sinus rhythm with atrial premature beats after acetyl strophanthidin.

difference between the P-R intervals in E_A and in right chest leads, the diagnosis of interatrial dissociation has been made in several cases.[3,56-60]

Sinus Arrest.—This arrhythmia is generally easily recognized in conventional leads. However, the proof of prolonged sinoatrial standstill requires esophageal records, especially if phonocardiograms and phlebograms are not available or are inconclusive.[61]

Atrioventricular Rhythms.—

Nodal rhythm: Esophageal electrocardiograms are necessary only when P waves are not well shown in other leads. P waves of middle nodal rhythm which are concealed within QRS complexes elsewhere are easily found in E_A.

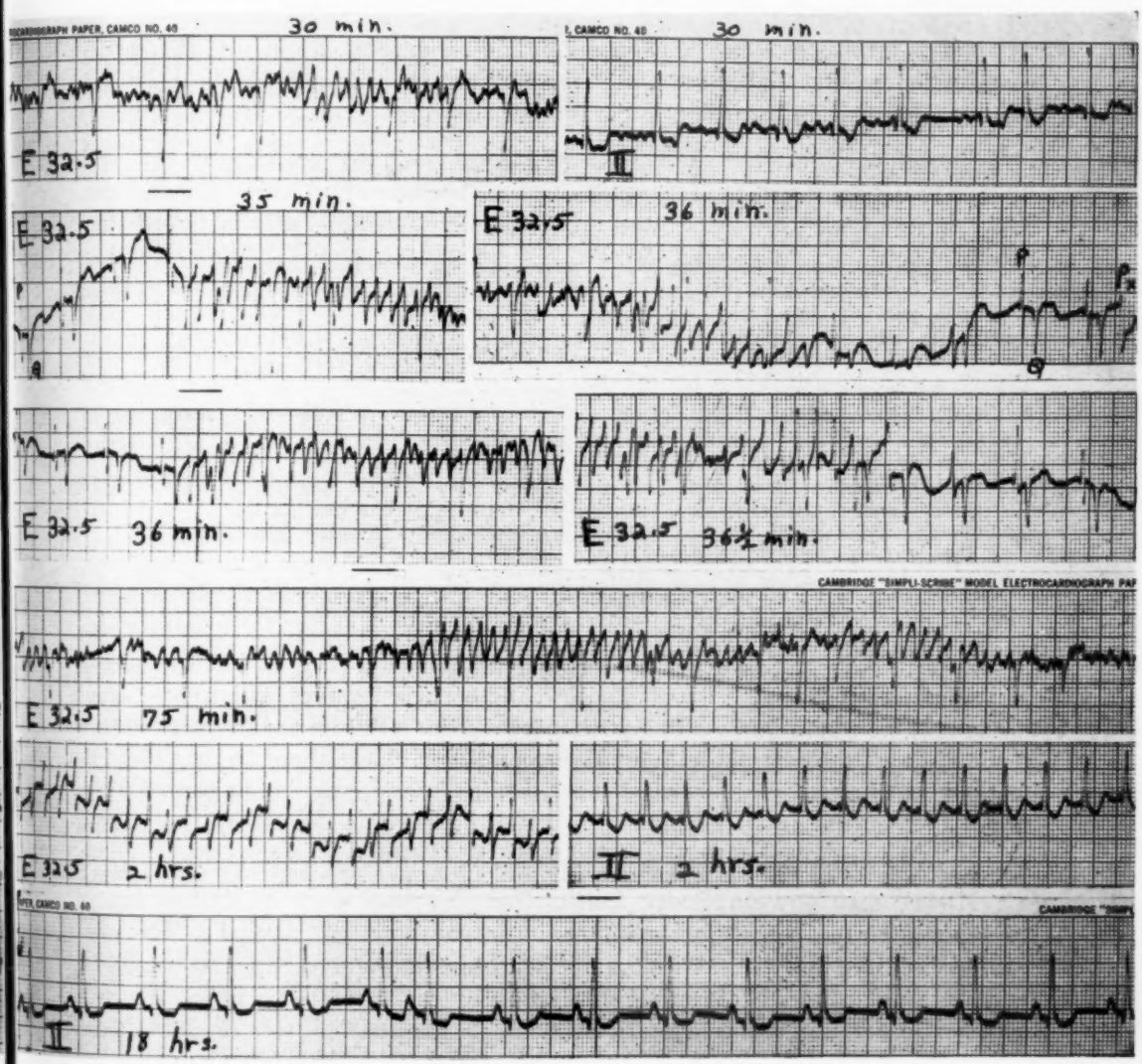

Fig. 15 (Case 87).—Atrial fibrillation reverting to sinus rhythm and recurring several times (upper four rows). Reappearance of flutter (fifth row) and restitution of sinus rhythm by digoxin (sixth row).

Good esophageal records of upper, middle, and lower nodal rhythm have been published.[35]

Interference dissociation: This arrhythmia is usually apparent from inspection of conventional leads, and esophageal leads merely serve to emphasize the independence of the P waves from the QRS complexes. In the complex case esophageal recording is essential to clarify the arrhythmia (Case 61, Fig. 5).

Atrioventricular Block.—E_A records are indicated in known cases of heart block when critical examination of T_a waves is desired. Such records may also be used to determine whether slow ventricular rates are due to extreme sinus bradycardia (as in one of our patients with a rate of 32) or to 2:1 block with alternate P waves concealed in the T waves in conventional leads.

Wolff-Parkinson-White Conduction.—The apparent origin of the QRS complex before the very end of the P wave is seen in other published esophageal records[62,63] and in intracardiac tracings as well.[64]

Premature Systoles.—Esophageal electrocardiograms permit instant and unequivocal recognition of P waves by virtue of their amplitude and sharpness. The origin of the premature beats can then be determined by observing whether atrial rhythm or excitation is altered. By this method middle nodal premature systoles and cases of frequent atrial premature systoles simulating atrial fibrillation may be unmasked.[63]

In three of our cases of atrial premature systoles, some of the postextrasystolic P waves were identical in size and shape to the ectopic ones. This phenomenon has been described by Lewis.[65] He attributed it to a physiologic hastening of impulse formation by the discharge of the premature systole at the focus of origin, so that the latter actually beats out the sinus node in producing the next impulse. E_A records can reveal this situation better than conventional leads.

Paroxysmal Tachycardia.—

Sinus: A case of paroxysmal sinus tachycardia with 2:1 atrioventricular block similar to ours and investigated by esophageal leads has been described.[23]

Atrial: Our two patients with 1:1 conduction had reversal in form of the atrial complexes (negative P waves at low, and positive P waves at high esophageal levels). This would imply a low atrial pacemaker. Despite the frequent occurrence of atrial tachycardia without atrioventricular block, there are surprisingly few published esophageal records. Two definite cases appear in one communication.[66] Other published cases might better be classified as supraventricular, since a nodal origin cannot be excluded from the evidence shown.[66,67]

Atrial, with atrioventricular block: Our six cases were clinically similar to other reported cases of this interesting arrhythmia[10,23,65,68-75]; i.e., the paroxysms occurred in patients with organic heart disease, were resistant to quinidine, and were not converted to atrial fibrillation by digitalis. This type of tachycardia is often unrecognized and considered to be atrial flutter or fibrillation, depending upon the variability of the associated atrioventricular block. Esophageal electrocardiography has particular value in this disorder. The diagnostic

criteria in E_A are as follows: (1) rapid and strictly regular P waves of identical form, (2) variable ventricular rate and rhythm, according to the grade and constancy of atrioventricular block, and (3) isoelectricity of P-P intervals where they are devoid of QRS-T complexes. This should be demonstrated at several atrial esophageal levels.

Supraventricular: In our case it was impossible to decide whether the focus was atrial or upper nodal, for the form of the P wave and the duration of the P-R interval were borderline.

Nodal: The case in the present series was thought to be one of upper nodal tachycardia because of a small P wave and a short P-R interval. The appearance in E_A of middle or lower nodal tachycardia is not always unequivocal. Even though it is possible to disclose P waves which are elsewhere completely concealed, it may be difficult to determine whether they are normal or retrograde in form. This is particularly so when E_A reveals a thin P inscribed upon a steep R or S deflection. Several published records exemplify this difficulty,[66,67,76] whereas another is unequivocal.[62]

His bundle and ventricular: The differentiation between these tachycardias is difficult except on the basis of degree of ventricular aberration. E_A records in both types are capable of revealing otherwise obscure P waves, thus establishing the independence of atrial activity in the usual cases where there is no backward conduction. In the rare type, with retrograde conduction to the atria, P waves should be negative at low and positive at high esophageal levels. There are few published esophageal electrocardiograms of ventricular tachycardia,[66,76-78] and it is possible to regard some of them as equivocal because they fail to show independent atrial activity[66] or unquestionably retrograde P waves.[78]

Atrial Flutter.—Our nine cases displayed the same features in E_A as other published cases.[23,35,38,76,79,80] These features are so constant that they constitute rigid criteria for the diagnosis of atrial flutter, as follows: (1) rapid and precisely regular atrial complexes of identical form, (2) variable ventricular rate and rhythm, and (3) *absence* of *isoelectric P-P intervals.*

The last characteristic is uniformly shown as broad ascending lines starting just before the end of one P wave and terminating at the beginning of the following P wave. It is important to realize that this is not necessarily present at all atrial levels (see Case 15), and it is therefore essential to make records from many levels.

Probably the commonest application of esophageal electrocardiography in arrhythmias is in the differentiation of the tachycardias and especially in distinguishing between atrial tachycardia with block and atrial flutter. This distinction is based upon the appearance of the P-P intervals as already described.[10,23,71,74] Although flutter oscillations are common in standard leads and usually present in chest leads, there are cases of atrial flutter in which P-P intervals are isoelectric in these leads.[10] Recourse must then be had to esophageal electrocardiograms. This was the situation in three of our cases, two of which are described (Cases 6 and 15).

It has been stressed that the intrinsic deflections of the atrial complexes during flutter imply coordinated contractions.[23] The extent of these contractions is shown by recent methods of recording pressure variations within the right atrium.[81] The pressures during atrial flutter have been found to range between 0 to 10,[82] 2 to 7,[83] and 9 to 15 mm. Hg.[83]

The characteristics of atrial flutter in esophageal leads are strikingly similar to those in intracardiac leads.[41] The author had the opportunity to examine the intra-atrial electrocardiograms of three patients with atrial flutter and found that in each case there was at least one site from which the typical ascending P-P intervals could be recorded.

The absence of isoelectricity reflects the belief that during flutter "some portion of the atrial muscle is always in systole (in the electrical sense)."[1] Indirect evidence in support of the circus theory has been derived from the simultaneous recording of esophageal and other leads in cases of atrial flutter,[23,79,80,85] the results implying that a constantly circulating wave is present.

Recent investigations[86,87] throw doubt upon the validity of the circus theory and favor the simpler explanation that flutter is due to repetetive discharges from a single focus and that it differs from atrial tachycardia by virtue of a higher rate and a tendency to atrioventricular block. Prinzmetal's high-speed motion pictures appear to demonstrate this clearly, at least so far as the passage of the muscular contraction wave is concerned. Prinzmetal[88] believes that the undulating base line between P waves represents distorted atrial T waves; that as the rate of atrial tachycardia increases and approaches that of flutter, isoelectric P-P intervals are gradually replaced by increasingly deformed T_a waves which take on a characteristic form when atrioventricular block appears. This contention is not borne out in some esophageal records. For example, small T_a waves of the usual form may occasionally be seen in E_A leads in atrial flutter (Fig. 11) and were seen in the intra-atrial leads of two cases mentioned previously. These T_a waves are separate and distinct from the general slope of the P-P intervals.

That the rate alone is not the critical factor in distinguishing atrial flutter from tachycardia is apparent on clinical grounds. Cases of flutter are seen with atrial rates slower than those usually found in tachycardia, especially during quinidine treatment (Case 15). It is therefore probable that the problem of the mechanism of atrial flutter is not yet resolved.

Atrial Fibrillation.—E_A records of our cases were similar to those of published cases[23,37] and demonstrate that esophageal leads seldom yield larger or sharper atrial waves than do right chest leads. Of interest, however, is the occasional occurrence of atrial complexes with intrinsic deflections, as in two of our patients. Whether this denotes the existence of a circulating mother wave and a tendency to spontaneous reversion[23] is doubtful,[37] although one of our patients (Case 87) reverted to normal rhythm several times. Each time, another bout of fibrillation was set off by an atrial premature systole, a phenomenon long known, though rarely recognized.[89] Intrinsic atrial deflections have been recorded during fibrillation by direct epicardial leads in animals[1] and by intra-

atrial leads in man.[43] Their presence may signify that the circulating wave has a less fractionated path than usual,[90,91] resembling a flutter path more closely. It is interesting to speculate whether the presence of intrinsic deflections in atrial fibrillation implies a greater likelihood of dislodgment of mural thrombi since the intrinsic deflections probably indicate coordinated atrial contractions.

Right chest leads in atrial fibrillation occasionally yield large atrial waves (in our experience up to 0.7 mv.), and these may occasionally give the impression of regularity. Indeed, in certain publications which show only short strips of the electrocardiograms it is difficult to distinguish such records from those of atrial flutter,[6,8,41,73,92] unless it is borne in mind that in flutter the atrial rhythm is so precisely regular that variations in cycle length are too small to be detected by the unaided eye.[93]

With these facts in mind, attention is called to reports of a group of curious arrhythmias designated as examples of interatrial dissociation resulting in flutter of the right atrium and fibrillation of the left.[3,57,59,94,95] The diagnosis is based upon the finding of flutter waves in right atrial exploratory leads and fibrillary waves in left atrial exploratory leads. However, close inspection of the published records does not permit acceptance of the evidence as conclusive. The atrial waves in right chest leads display minor variations in form and rate in some cases[57,59,94]; in one instance needle electrodes on the anterior and posterior thorax were claimed to be exploratory for the left atrium,[3] and in another case only a single esophageal level was recorded.[95] The last case may possibly have been atrial flutter and the absence of atrial deflections in the esophageal lead may have been due to the fact that the optimal level was not recorded. In the author's opinion these cases are probably examples of atrial fibrillation in which the path was at times more regular than usual, thus superficially resembling flutter.

CASE REPORTS

The following case reports are given as examples of the practical clinical application of esophageal electrocardiography to the differential diagnosis of cardiac arrhythmias.

CASE 6.—A 60-year-old man with hypertensive heart disease was admitted with the complaint of rapid heart action for several days. Conventional electrocardiography showed the pattern of left ventricular hypertrophy and an apparent sinus tachycardia with occasional ventricular premature beats (Fig. 10). Esophageal records disclosed an atrial rate of 250 with 2:1 conduction and occasional premature ventricular beats. When the latter occurred, it was possible to see two P waves in succession undisturbed by ventricular complexes. This permitted observation of the characteristic ascending P-P interval of flutter and thus established the diagnosis. Ten hours after combined ouabain-digitalis leaf administration, another examination showed normal rhythm.

CASE 15.—A 56-year-old man had persistent atrial flutter during four years of observation. This probably dated back to an attack of posterior myocardial infarction about a year before he first came under observation. The arrhythmia was resistant to many trials of intensive quinidine and digitalis therapy, although the latter easily controlled the ventricular rate. Esophageal electrocardiograms in September, 1947 showed an atrial rate of 207 (Fig. 11). Tracings were made at only two levels, 37 and 40 cm. Neither of these revealed the characteristic P-P intervals. Attention is called to the presence of well-marked T_a waves in E_{37}. In June, 1948, esophageal

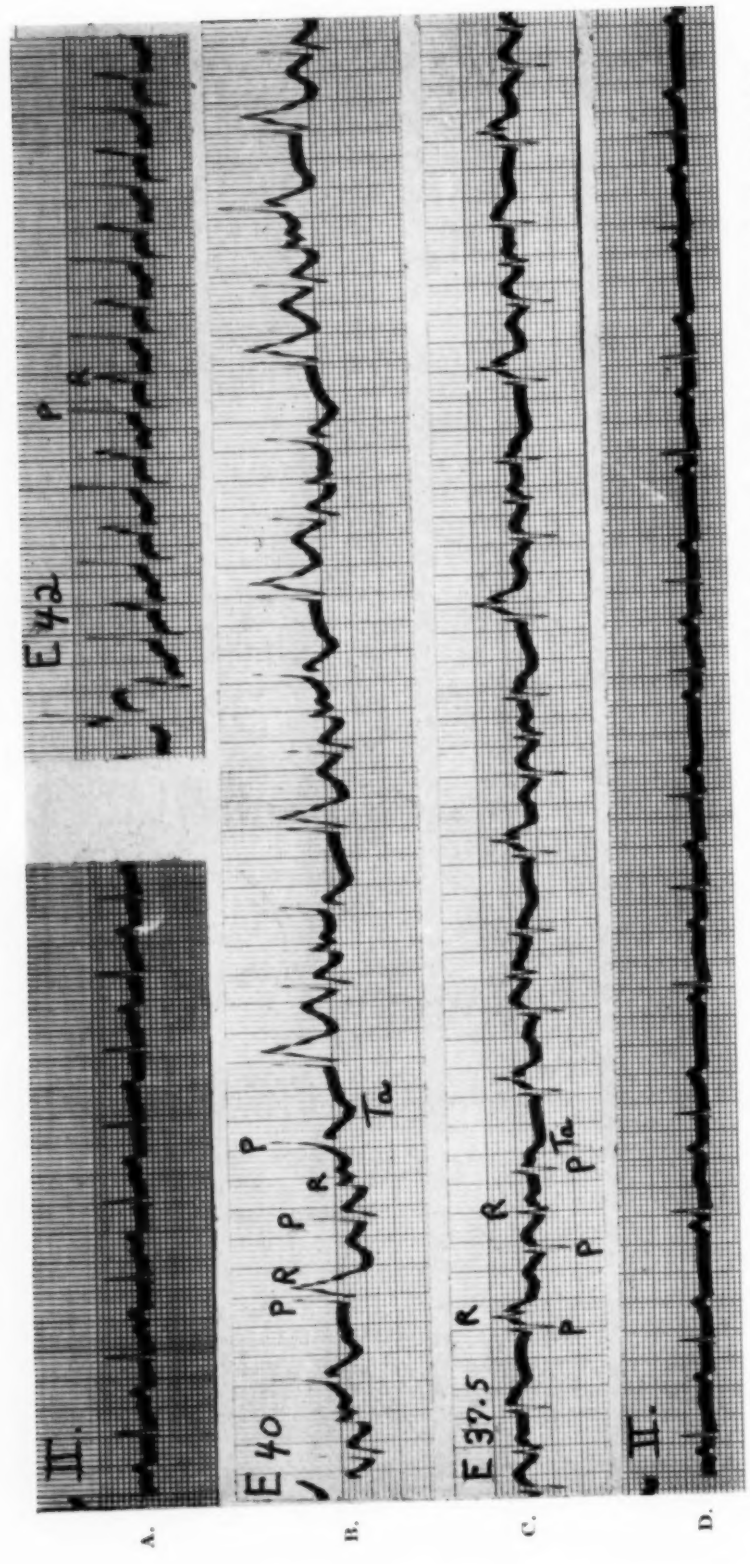

Fig. 16 (Case 45).—Sinus tachycardia and incomplete atrioventricular block. Note the very short P-R interval at the beginning of each Wenckebach period in E_{40} (see text).

records were obtained from many levels (Fig. 12), and typical ascending P-P intervals were found at several levels. In January, 1950, a deliberate attempt was made to obtain maximal slowing of the atrial rate by giving 0.4 Gm. of quinidine every two hours. After a total of 3.2 Gm., the atrial rate slowed to 136, at which time the ventricular rate was 55 and the QRS complex duration was 0.14 second. No esophageal record was made at this time. A few hours later the atrial rate was 220. A week later the experiment was repeated when the atrial rate was 212. After a total of 2.8 Gm. of quinidine, bizarre ventricular complexes appeared. These changed in form and became regular, at which time another esophageal record was made (Fig. 13). The latter revealed atrial flutter with 1:1 conduction and extreme aberration of ventricular complexes, the rate being 150. In the illustration it is seen that the R wave precedes the P wave and the ascending P-P intervals are somewhat marred by ventricular T waves. In a few hours, quinidine having been stopped, the electrocardiogram returned to its usual appearance.

CASE 45.—A 55-year-old man with arteriosclerotic heart disease was given 1 mg. of neostigmine intravenously in order to observe the effects on conduction. Initially, he had sinus tachycardia and a P-R interval of 0.22 second. Following the neostigmine he developed an increase in the grade of atrioventricular block with Wenckebach periods (Fig. 16). However, for a few seconds, a puzzling arrhythmia appeared (Fig. 16,*B*). The first R wave of each Wenckebach period occurred after a P-R interval of only 0.05 second and was grossly aberrant in form. The explanation is not evident. It may represent a remarkably constant ventricular escape after each dropped beat, or it may possibly be due to a mechanical effect of atrial contraction.[95]

CASE 56.—A 60-year-old man with arteriosclerotic heart disease entered the hospital with a ventricular rate varying from 30 to 40. Conventional electrocardiograms showed regular, rapid atrial activity and slow and irregular ventricular beats. In the course of nine days the atrial rate spontaneously declined from 188 to 158 while the ventricular rate remained unchanged. Esophageal records (Fig. 8) demonstrated a high grade of atrioventricular block and an absence of oscillations between P waves at all levels in steps of 2 to 2.5 cm. from 55 to 32 cm. The mechanism was therefore judged to be atrial tachycardia with block. In the next two weeks sinus bradycardia with a P-R interval of 0.36 second appeared. Eleven months later, while this manuscript was being prepared, the patient returned with similar findings. The atrial rate declined from 200 to 187 in a week, without treatment, and another esophageal examination disclosed the same situation—atrial rate 187, ventricular rate 36 to 39. After 2 mg. of atropine given intravenously the atrial rate was unchanged, and the ventricular rate rose to 52 to 65. A week later, the arrhythmia was replaced by sinus bradycardia with a P-R interval of 0.44 second and occasional sinus arrests.

CASE 61.—A 62-year-old woman with arteriosclerotic heart disease exhibited frequent sinus arrests followed by a complex arrhythmia after some of the escapes. These episodes were reproducible upon administration of several digitalis preparations (Fig. 4). Esophageal leads showed that after a few periods of sinus arrest followed by escapes from a nodal center, an unusual form of interference dissociation became established (Fig. 5). This consisted of an independent sinus rhythm varying in rate from 52 to 55, a ventricular rhythm of nodal origin varying in rate from 65 to 71, and additional conducted beats from the sinus node after alternate ventricular beats, so that the total ventricular rate was 90. It was apparent that the nonconducted sinus beats occurred while the junctional tissues were refractory, thus giving rise to alternate pseudoreciprocal rhythm. This arrhythmia could not have been analyzed with certainty from standard leads alone. An arrhythmia with similar features has been recently reported.[97]

CASE 86.—A 40-year-old man with heart disease of unknown origin gave a history of rapid arrhythmias since early childhood. In the year before admission, these became more frequent and of longer duration. A month before admission he sustained a cerebral lesion, believed to be an embolus, while on quinidine therapy. The upper two rows of Fig. 6 show an esophageal and a limb lead mounted as though they were recorded simultaneously to facilitate location of the P waves in the latter. It is seen that the irregularity consisted of groups of normal and premature beats, the latter most probably arising from the bundle of His. The lower portions of Fig. 6 show the appearance of sustained tachycardias, all of which arose from the same focus, namely the bundle of His.

CASE 87.—A 70-year-old man, while being treated for bronchopneumonia, was discovered to have atrial flutter with 2:1 conduction. His response to a rapid-acting digitalis preparation is shown in Figs. 14 and 15. Many abrupt changes of rhythm occurred during the first two hours. Of interest is the mechanism of atrial fibrillation set off by atrial premature beats, as shown clearly in the tracings thirty-five and thirty-six minutes after the injection. When the drug wore off, the original flutter returned. The patient was then given 1.5 mg. of digoxin orally, and the next morning normal rhythm with occasional atrial premature beats was present. This is believed to be the first esophageal record showing the onset and offset of atrial fibrillation and the relation between the common atrial arrhythmias.

SUMMARY AND CONCLUSIONS

1. Esophageal electrocardiograms were made 111 times in ninety-eight cases comprising a large variety of arrhythmias, and their appearance was described.

2. The appearance of the P wave in the esophageal electrocardiogram is remarkably distinct and uniform in all cases in which there is coordinated activity of the atria.

3. The amplitude and sharpness of esophageal P waves permit instant recognition and certain analysis of atrial activity, thereby aiding in the differential diagnosis of arrhythmias.

4. The end deflection of the atrial complex, the T_a wave, can be studied to great advantage by this method in certain cases.

5. The esophageal electrocardiogram is of practical importance, particularly in distinguishing atrial tachycardia from flutter when the appearance in other leads is equivocal.

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THE NATURE OF THE RS-T SEGMENT DISPLACEMENT AS STUDIED WITH ESOPHAGEAL LEADS

Left Ventricular Hypertrophy

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In left ventricular hypertrophy due to hypertension, aortic valvular diseases, or other causes, there is a progressive sequence of electrocardiographic changes which vary with the progression of the hypertrophy and the degree of myocardial involvement.[1-6] In the beginning, a left axis deviation is usually present, which is due mainly to a horizontal electrical axis of the heart. Increased voltage of the QRS deflections and alterations in the T waves may be noted in the standard and unipolar precordial leads. Later, there may be a further increase in the amplitude of the QRS complexes, and the T waves become more inverted. The RS-T segment becomes increasingly depressed, especially in the left precordial leads. Elevations of the RS-T segment may be seen in leads taken over the right precordium. In the presence of marked left ventricular hypertrophy, the duration of the QRS complex may be prolonged up to 0.11 second or more, and the intrinsic deflection is usually delayed in Leads V_5 and V_6.[7,8]

The increase in amplitude and duration of the QRS complexes has been related to the hypertrophy and/or dilatation of the left ventricle.[1,2,3,5,9,10] The causes for the RS-T segment deviations in cases of left ventricular hypertrophy are not generally agreed upon, and various explanations have been suggested. These changes have been attributed by some investigators to the hypertrophy of the left ventricle,[1,3,4,5,11] to a state of chronic coronary insufficiency,[12,13,14] and to repolarization or regression deviations.[15,16,17]

Esophageal electrocardiograms taken at a certain level of the left atrium have been shown to reflect left ventricular cavity potentials, and leads taken below the atrial level record the potentials of the posterior surface of the heart.[18,19] In a previous study it has been shown that in induced coronary insufficiency the RS-T segment depressions as recorded in standard precordial leads were consistently associated with the RS-T elevations in esophageal leads reflecting left ventricular cavity potentials.[20] This indicated that the RS-T deviations were probably due to involvement of the subendocardial aspect of the heart with a resultant transient current of injury.

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Esophageal leads thus offer a simple method of studying left ventricular cavity potentials without resorting to more complex procedures such as catheterization of the left side of the heart. The use of esophageal leads in studying the RS-T segment displacement inside the left ventricular cavity also avoids the possible RS-T deviation caused by the contact of the tip of the intracardiac electrode with the endocardium. In the present study, the simultaneous recording of esophageal leads with standard and unipolar extremity and chest leads was employed to investigate the nature of the RS-T segment deviations in patients with left ventricular hypertrophy.

METHODS

Eleven patients were selected because of fluoroscopic and x-ray evidence of enlargement of the left ventricle and electrocardiographic changes indicative of left ventricular hypertrophy. In these patients, persistent RS-T segment depressions were present with and without T-wave changes. Only one patient gave a history of angina on effort, and none of the patients had ever received any digitalis preparations. Seven of the patients had hypertensive heart disease; two had arteriosclerotic heart disease; two had rheumatic heart disease with aortic valvular involvement. The ages of the patients ranged from 35 to 66 years of age.

The details of the methods employed in this study have been described elsewhere.[20] Briefly, an esophageal lead, consisting of a fine rubber tube containing a central core of fifteen fine wires, each separately connected to external metal bands, was passed under fluoroscopic control to approximately 6 cm. below the diaphragm into the fundus of the stomach. Simultaneous standard, unipolar precordial, and esophageal leads were taken with a Technicon three-channel direct-writing cardiograph with the aid of an electrical filter[21] and an external selector.

In three cases, simultaneous electrocardiograms were taken before and immediately after the "two-step" exercise test.[22]

In all cases, the magnitude of the manifest ventricular gradient ($\hat{G}$) and its direction ($\hat{G}$) in the frontal plane were calculated according to the methods of Ashman, Byer, and Bayley.[17,23] In six additional cases where serial electrocardiograms were available over a period of five to fifteen years demonstrating the progression of changes from normal to left ventricular hypertrophy, the magnitudes of the manifest ventricular gradients and their directions were measured and the degree of change recorded.

RESULTS

In all cases, the RS-T segment depressions seen in standard, precordial, and esophageal leads reflecting the potentials of the posterior surface of the heart were associated with RS-T elevations in esophageal leads reflecting left ventricular cavity potentials (Figs. 1 to 3). In almost every instance the esophageal leads reflecting the posterior and diaphragmatic surface of the left ventricle showed more marked depression of the RS-T segment than that seen in either the precordial or standard leads (Figs. 1 to 3).

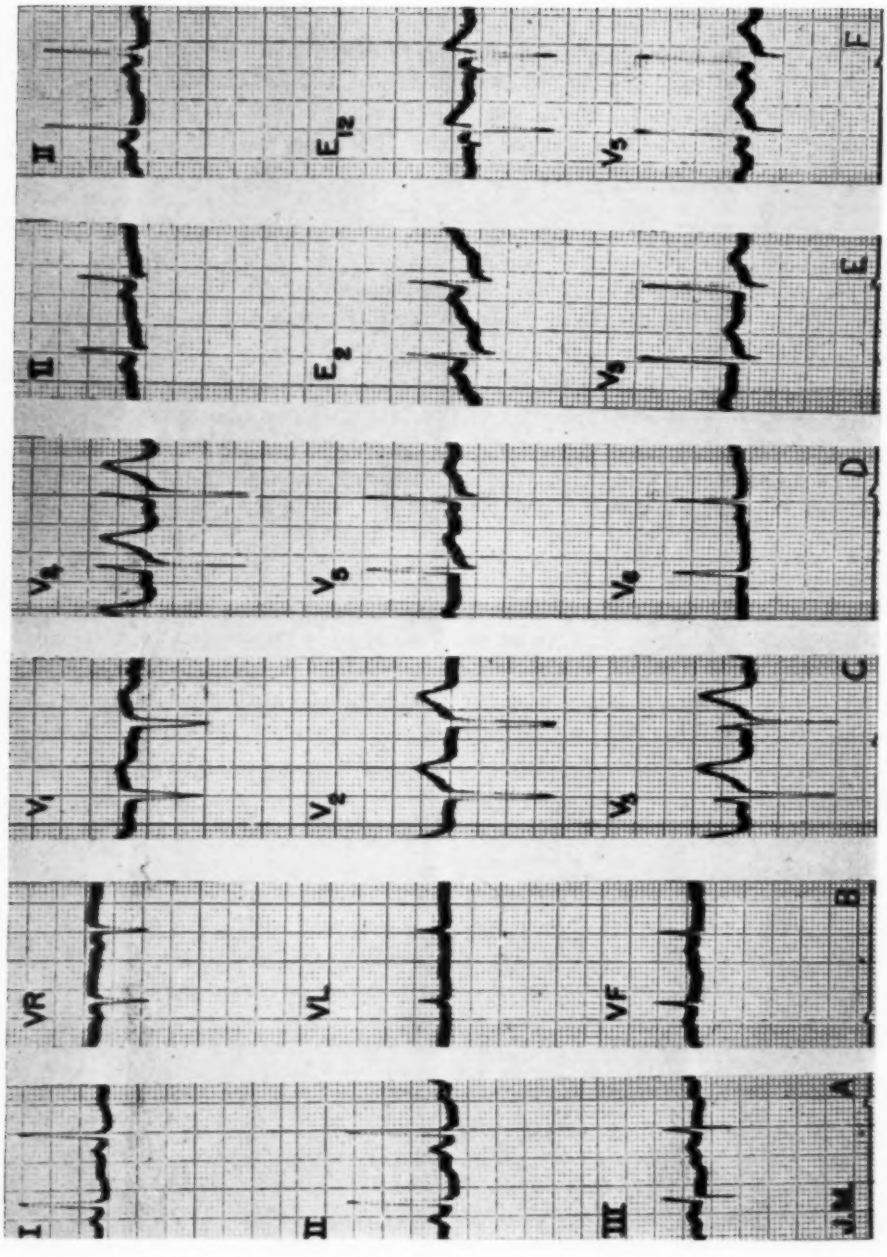

Fig. 1.—J. M., a patient with left ventricular hypertrophy with RS-T segment depression and flattened or upright T waves in Leads V_5 and V_6. The RS-T segment depression is more marked in E_2 (esophageal lead reflecting posterior surface of left ventricle) than in left precordial leads. In E_{12} (esophageal lead reflecting left ventricular cavity potentials) note the elevation of the RS-T segment and inversion of the T wave. V_B also shows some slight elevation of the RS-T segment. (All leads were standardized at 1 mv. = 10 mm. except *C*, *D*, *E*, and V_5 in *F* which were recorded at 1 mv. = 5 mm.)

at 1 mv. = 10 mm. except *C*, *D*, *E*, and V_5 in *F* which were recorded at 1 mv. = 5 mm.

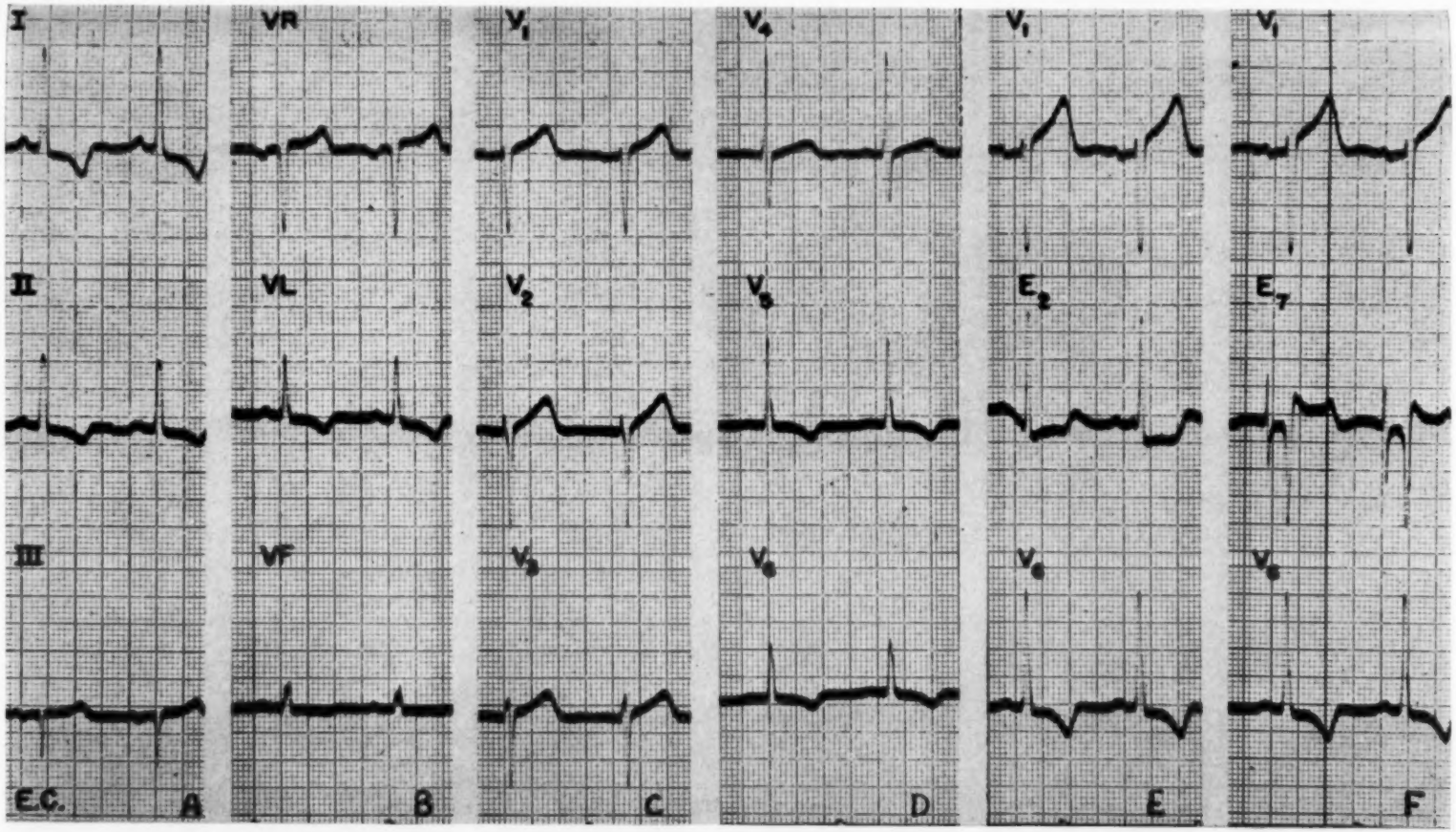

Fig. 2.—E. C. The RS-T segment depression and T-wave inversion in standard, left precordial, and lower esophageal (E_2) leads are associated with RS-T segment elevation and upright T wave in Lead E_7 (reflecting left ventricular cavity potentials). Note the RS-T segment elevation and upright T wave in V_R. A prominent intrinsic atrial deflection is seen in E_7. (All leads were taken at 1 mv. = 10 mm. except *C* and *D*, which were recorded at 1 mv. = 5 mm.)

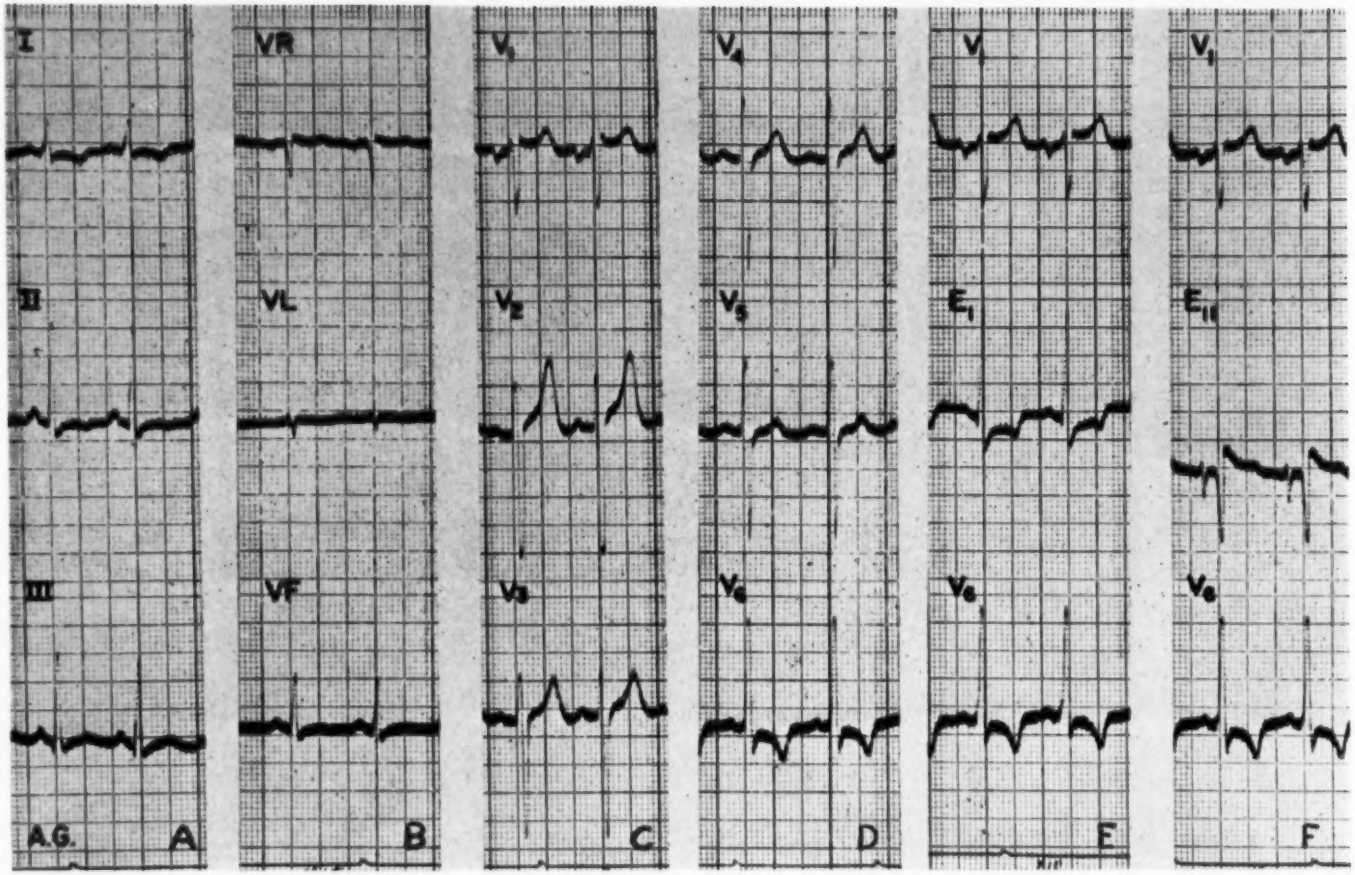

Fig. 3.—A. G. Note the more marked RS-T segment depression in E_1 than in the standard leads and V_6. Note the intrinsic atrial deflection in E_{II}. In this lead, which reflects left ventricular cavity potentials, the RS-T segment and T wave are opposite in direction to that seen in Leads V_6 and E_1. V_R shows a slightly elevated RS-T segment and upright T wave. (All leads were standardized at 1 mv. = 10 mm.)

After exercise, the RS-T segment in three cases showed a marked increase in the depression recorded precordially and in the elevation recorded at the atrial level. In the lower esophageal leads reflecting the posterior surface of the heart, the ventricular complexes were usually R, rS, or qR in configuration. In esophageal leads reflecting left ventricular cavity potentials, the ventricular pattern was QS or Qr in configuration and was usually associated with a diphasic intrinsic atrial deflection (Figs. 1 to 3). In no instance was an initial R wave encountered in esophageal leads reflecting the potential of the left ventricular cavity.

Generally, the direction of the T wave as seen in the left precordial leads was opposite to that found inside the left ventricular cavity. In those three cases where the T waves were upright in precordial leads, inverted T waves were recorded in esophageal leads reflecting left ventricular cavity potentials (Fig. 1). In the remaining eight cases where the T waves in the precordial leads were inverted, upright T waves were recorded from inside the left ventricular cavity (Figs. 2 and 3).

In the right precordial leads (V_1 to V_3) the RS-T segments were usually slightly elevated and the T waves upright (Figs. 1 to 3). In Lead V_R the RS-T segments were usually displaced upward, and in those instances where the left precordial T waves were inverted, the T waves were isoelectric or upright (Figs. 2 and 3). In those three instances where the T waves were upright in Leads V_5 and V_6, V_R showed inverted T waves (Fig. 1).

In these three instances the magnitudes of the manifest ventricular gradient ($\hat{G}$) and their directions ($\hat{G}$) were within normal limits. In five of the eight remaining cases, the gradients were definitely abnormal in direction (-8 degrees to -90 degrees) but were essentially normal in magnitude.

In six cases where multiple records were available over a period of five to fifteen years, the gradient in each record remained within the range defined as normal, except for one patient who showed an abnormal deviation to the left. The latter patient was in failure. It is noteworthy that in the case of hypertension observed over a period of fifteen years where the electrocardiogram progressively changed from a normal to a marked left ventricular hypertrophy pattern with RS-T segment depressions and inverted T waves in standard and left precordial leads, the direction and manifest magnitude of the gradient remained within normal range.

DISCUSSION

From the data presented above, it is evident that the RS-T segment depressions in the standard, precordial, and lower esophageal leads reflecting the posterior and diaphragmatic surfaces of the heart were consistently associated with RS-T segment elevations in esophageal leads reflecting left ventricular cavity potentials (Figs. 1 to 3). The degree of elevation of the RS-T segments inside the left ventricular cavity was proportional to the degree of the RS-T segment depression recorded in the standard and left precordial leads. The more marked RS-T depressions recorded in the lower esophageal leads than in the standard and left precordial leads were probably due to the proximity of the esophageal leads

to the surface of the left ventricle. The RS-T elevation and T-wave changes observed in V_R in the cases studied may be partly due to the influence of the left ventricular cavity potentials.

Normally the impulse originates in the sinoauricular node and spreads across the auricles and reaches the atrioventricular node. It then traverses the bundle of His and its branches. The impulse is then dispersed over the Purkinje network and is finally propagated through the myocardium from the endocardial to the epicardial surfaces of the heart.[24] The impulse reaches the uppermost part of the interventricular septum first, with the left portion of the septum probably being activated before the right, so that the wave of depolarization proceeds from left to right, resulting in initial negativity of the left ventricular cavity. The presence of a QS pattern inside the left ventricular cavity by direct catheterization of the left ventricle in dogs[25,26,27] and in man[28,29] and by esophageal leads at atrial levels in man[18,20,30] indicates that the left ventricular cavity is negative throughout the spread of the excitation process in the heart. In a large group of normal individuals studied by us with esophageal leads, whenever the RS-T segments were isoelectric in the standard, left precordial, and lower esophageal leads reflecting posterior surface potentials, it was found that the RS-T segments were also isoelectric in esophageal leads reflecting left ventricular cavity potentials. The direction of the T waves in the left ventricular cavity was opposite to that seen in left precordial leads.

In all of the cases of left ventricular hypertrophy studied, the presence of a QS pattern in esophageal leads reflecting left ventricular cavity potentials, indicating negativity inside the left cavity, and the simultaneously recorded positive R or qR complexes in the precordial leads demonstrated that the spread of the excitation wave is identical to that encountered normally. These observations are similar to those obtained in human subjects by catheterization of the left side of the heart in patients with left ventricular hypertrophy[29] and by esophageal leads at atrial levels recorded by others.[30,31,32]

The nature of the persistent RS-T depressions in patients with left ventricular hypertrophy has been the subject of much controversy, and many explanations have been put forth to explain these findings. Although these RS-T deviations are of a chronic nature, they are by no means always irreversible, since many patients have reverted to normal after sympathectomy or rice diet in cases of hypertensive heart disease.[3,7,33,34]

According to some investigators, the RS-T deviations and T-wave changes in patients with left ventricular hypertrophy are due to a delay in excitation of the left ventricle as a result of lengthening of the conduction pathway incident to the enlargement of the left ventricle.[3,11] Weber regarded the left ventricular preponderance electrocardiogram as an expression of "Linksverspätigung der Erregung," which he attributed to a state of chronic coronary insufficiency.[12,13] These changes have also been attributed to actual impairment in the conduction system of the left ventricle.[1,3,4,5,35] It has been suggested that the electrocardiographic pattern of left ventricular hypertrophy and that of left bundle branch block represent merely different degrees of retarded conduction in the left ventricle, since both conditions are usually associated with an enlarged left

ventricle, and since patients with left ventricular hypertrophy have gone on to develop an electrocardiographic pattern of left bundle branch block.

If the left ventricular hypertrophy pattern were due to a defect in the conducting system, it would be expected that the duration of the QRS complex would be substantially prolonged in patients with left ventricular hypertrophy, as in patients with left bundle branch block. Although the width of the QRS complexes may be increased in some cases of hypertrophy, the duration of the QRS complexes in this present study and in those reported by others was essentially within normal limits.[1,4,14,35-38] Furthermore, studies of left ventricular cavity potentials in cases of left bundle branch block by esophageal leads or by direct catheterization of the left side of the heart in man have revealed that the spread of conduction is different from that seen in patients with left ventricular hypertrophy.[28,39] In the latter, as already stated, the left ventricular cavity potentials are negative and represented by a QS complex. In left bundle branch block, the right side of the septum is activated ahead of the left side, and the wave of depolarization spreads from right to left. Hence, the left cavity potentials are initially positive as evidenced by an RS pattern.[28,39] Whereas the RS-T segment depressions recorded in V_5 and V_6 in patients with left ventricular hypertrophy were associated with RS-T segment elevations inside the left ventricular cavity, the RS-T depressions in patients with left bundle branch block were always associated with RS-T segment depressions in esophageal leads reflecting left ventricular cavity potentials.[39] Recently, the opportunity presented itself to record the transition from normal conduction to that of left bundle branch block and vice versa simultaneously in precordial leads and esophageal leads reflecting left ventricular cavity potentials.[40] In this case it was repeatedly demonstrated that the negativity of the left ventricular cavity during normal conduction changed to initial positivity as seen by the change from a QS to an RS pattern when varying degrees of left bundle branch block supervened. The isoelectric RS-T segment during normal conduction became depressed in both the precordial and esophageal leads reflecting the left ventricular cavity potentials when the conduction changed to that of left bundle branch block.[40] From these observations it is evident that the QS pattern obtained in the left ventricular cavity in left ventricular hypertrophy represents a normal pathway of conduction as contrasted with the pathway of conduction in various stages of incomplete or complete left bundle branch block where initial positivity is recorded. Therefore, in left ventricular hypertrophy, the electrocardiographic pattern is not due to delayed conduction in the left bundle branches.

More recently, Ashman,[16,17] utilizing the concept of ventricular gradient as put forth by Wilson, Macleod, Barker, and Johnston[15] attributed the RS-T segment deviation in left ventricular hypertrophy to repolarization or regression deviations. In the absence of a diseased myocardium, these deviations have been regarded as being normal physiological phenomena.[16,17] These RS-T changes were related to the relative magnitude of the manifest area of the QRS and of the ventricular gradient. In a study of ninety-six patients with the electrocardiographic pattern of left ventricular hypertrophy, the gradient was within normal range in sixty-four, abnormally deviated to the right in eleven

and to the left in eleven, and doubtful in ten.[41] Similar observations were recorded in a series of fifty-two patients by Michaelides and Costeas[42] who found 11.5 per cent with abnormal gradients. In both series, cases which showed abnormal deviation of gradient were associated with either T-wave changes suggesting myocardial ischemia or were found in subjects in the older age groups who had some evidence of coronary arteriosclerosis.[41,42]

In the present study, in the three patients in whom both the size and direction of the gradients were within normal range, the RS-T segment depressions were associated with upright or slightly flattened T waves in the left precordial leads. In these cases the hearts were only moderately enlarged, and the patients were relatively free of complaints. In the remaining eight patients the disease process was of longer duration, and the electrocardiograms were associated with more marked depression of the RS-T segment and inversion of the T waves in the left precordial leads. Among these patients, five of the eight showed definitely abnormal direction of the ventricular gradient. These observations, therefore, in accord with those of others,[41,42] would indicate that abnormal deviations of the ventricular gradient are apt to occur when the myocardium is involved.

The RS-T segment changes in most cases of early left ventricular hypertrophy (Fig. 1) are probably due to regression or repolarization deviations incident to the increase in muscle mass and are, therefore, of physiological origin. However, these changes are not always to be regarded as of normal physiological origin,[16,17] especially in long-standing cases of left ventricular hypertrophy. It is conceivable that the maintenance of a normal gradient in patients with left ventricular hypertrophy may also be due to a diffuse involvement of the myocardium with normal sequential pattern of repolarization maintained. This may explain the persistence of the normal gradient in some cases of long-standing hypertrophy with progressive RS-T and T-wave changes, as in the patient described in whom the electrocardiograms showing progressive changes were observed over a period of fifteen years.

In the presence of left ventricular hypertrophy there are many factors to be considered which may interfere with the process of repolarization and thus account for some of the RS-T segment deviations. These factors may produce metabolic disturbances in the individual heart fibers and never leave any permanent changes which could be recognized histologically. Some observers have attempted to explain the T-wave changes in hypertrophy on the basis of "metabolic strain" on the heart.[43] It has been shown by Wearn[44] that in hypertrophied hearts there is a marked discrepancy in the muscle-capillary relationship. As the heart enlarges, there is a decrease in the concentration of capillaries per unit area of muscle. The blood supply thus becomes insufficient and does not keep pace with the increase in muscle mass of the left ventricle. It was also shown[44] that as the heart enlarges, the distance from the capillary wall to the periphery of the muscle mass which it supplies becomes greater. Thus, the route over which oxygen has to diffuse and over which metabolic products have to travel increases in proportion to the degree of hypertrophy. The actual capillary surface available for exchange is also markedly decreased per unit mass of muscle.[44]

Furthermore, the increased thickness of the hypertrophied muscle cells may also interfere with the rapid diffusion of oxygen, nutriments, and metabolites in and out of the cells.[44,45] It is possible that in the heart, as in other tissues of the body, there is a wide range of physiological compensation for these metabolic disturbances. This would account for the not infrequent occurrence of normal resting electrocardiograms in early cases of left ventricular hypertrophy. However, a stage is ultimately reached when the metabolic processes are sufficiently impaired as to interfere with the process of repolarization of the heart. The fact that in some patients with left ventricular hypertrophy RS-T segment deviations and T waves may return to normal and remain so after sympathectomy without reduction in net QRS areas[7,33] is perhaps further evidence that these changes may at least in part be due to metabolic disturbances.

Depression of the RS-T segment with or without T-wave changes similar to those seen in some patients with left ventricular hypertrophy has been frequently encountered clinically in cases of anemia, severe hemorrhage, shock, and pulmonary embolism, during attacks of angina, and in induced anoxemia in normal and abnormal individuals.[46-51] RS-T segment and T-wave changes similar to those encountered in patients with left ventricular hypertrophy in standard, precordial, and esophageal leads reflecting left ventricular cavity potentials have been observed in induced coronary insufficiency after exercise.[20] In all these instances, the RS-T changes were of a transitory nature and reverted to the resting state after the precipitating factors had been removed. Such deviations have been attributed to transient myocardial ischemia, especially of the subendocardium.[20,50,51] That myocardial ischemia may be one of the important factors in the production of RS-T segment depressions precordially in some patients with left ventricular hypertrophy is evidenced by the increase in the degree of these changes after exercise in three cases already discussed. It has been shown that experimentally induced injury to the subendocardial surface of the left ventricle has produced elevation of the RS-T segment in leads from within the cavity of the left ventricle, while epicardial leads taken directly over the damaged subendocardial areas have shown RS-T segment depression.[31,52,53]

In patients with left ventricular hypertrophy associated with some degree of coronary insufficiency, T-wave changes are probably due to myocardial ischemia, with resultant disturbances in repolarization. As the degree of oxygen lack increases, the intensity of polarization of certain cell membranes decreases, and the ischemic condition then passes over to the state of injury, producing the RS-T segment changes.[54]

It is thus apparent that in attempting to explain the RS-T segment deviations in patients with left ventricular hypertrophy, there are many factors to be considered. Normally, the presence in man of a ventricular gradient which is probably due to earlier repolarization of the subepicardial layers of the heart accounts for the upright T waves. In early cases of left ventricular hypertrophy (Fig. 1), where the gradient remains within normal limits, the depressions seen in the standard, left precordial, and lower esophageal leads, which are regularly associated with RS-T segment elevations in leads reflecting the left ventricular cavity potentials, are probably due to delayed repolarization of the

subepicardial layers because of the increase in muscle mass, so that the subendocardium begins and completes its repolarization ahead of the subepicardium. Metabolic changes may further aggravate the repolarization deviations.

With progression of the hypertrophy and of the degree of myocardial involvement of the left ventricle due to superimposed coronary insufficiency, the inverted T waves and the increase in degree of RS-T depressions in standard and left precordial leads are probably best explained on the basis of myocardial ischemia and state of injury. The gradient of changes predominantly affects the subendocardial layers, as indicated by the associated elevations of the RS-T segment in esophageal leads reflecting the left ventricular cavity potentials (Fig. 2). It is in the presence of coronary insufficiency which leads to myocardial changes, chiefly localized to the subendocardium, that the direction of the ventricular gradient is most often abnormal.

SUMMARY

1. Eleven cases of left ventricular hypertrophy were studied with simultaneous standard, unipolar extremity, precordial, and esophageal leads. The magnitude and the direction of the ventricular gradient were determined in each case.

2. In left ventricular hypertrophy, the RS-T segment depressions seen in the standard, left precordial, and lower esophageal leads reflecting posterior surface potentials are regularly associated with RS-T segment elevations in esophageal leads reflecting left ventricular cavity potentials.

3. The T waves recorded in esophageal leads reflecting left ventricular cavity potentials are opposite in direction to those seen in the standard, left precordial, and lower esophageal leads.

4. The nature of the RS-T segment deviations in left ventricular hypertrophy is discussed.

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ELECTROCARDIOGRAPHIC STUDIES OF THE EFFECT OF HISTAMINE ON THE CARDIAC MECHANISM

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THE purpose of this paper is to report on the effect of lethal and sublethal doses of histamine (acid phosphate) on the hearts of guinea pigs and rabbits with respect to the cardiac mechanism, as revealed by electrocardiographic studies, and the tissue changes, as revealed by microscopic examination of the myocardium. This study includes also an investigation of the extent to which antihistaminics in the form of Benadryl (β—dimethylaminoethyl benzhydryl ether hydrochloride) interfere with or alter the changes referred to when administered either simultaneously with, or shortly before, histamine administration.

Since histamine is thought to play at least a partial role in anaphylaxis, the changes thus produced will be compared with those previously obtained by one of us[1] in the course of anaphylactic shock and experimental asphyxia in the guinea pig and the rabbit.

Anaphylactic shock is produced in part by the release of a histamine-like substance from the cells of the shock organ as a result of antigen-antibody union. The shock organ in the guinea pig is the smooth muscle of the bronchi and bronchioles. The histamine thus released produces in the guinea pig constriction of the smooth muscle of the bronchi and bronchioles so that the manifestations of anaphylactic shock are essentially those of asphyxia.[2,3] In the rabbit the shock organ is the media of the arterioles.[2,3] If the shock dose of antigen is injected intravenously, the antigen-antibody union takes place in the pulmonary arterioles with resulting constriction of these vessels. Anaphylactic shock occurs, therefore, as a result of the development of pulmonary hypertension with retrograde stasis and dilatation and failure of the right side of the heart, so that death is due actually to heart failure. The intravenous administration of lethal doses of histamine into guinea pigs and rabbits also produces fatal shock, the manifestations of which are in many ways indistinguishable from those seen in fatal anaphylactic shock. Hence, it is of some interest to determine the effect of large doses of histamine on the cardiac mechanism and the myocardium of normal unanesthetized guinea pigs and rabbits.

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PHARMACOLOGIC PROPERTIES OF HISTAMINE

Barger and Dale[4] were the first to isolate histamine from ergot. Later,[5] it was shown to be present in all organs, particularly in shock organs such as the liver, the intestinal wall, and the lung from which it may be obtained by alcohol extraction. Histamine is a decarboxylation product of histidine. The latter results from urea which is formed in the liver through the de-aminization of amino acids. Amino acids are derived from proteins. Pharmacologically, histamine produces reactions of widespread nature which vary somewhat with the species. It effects contraction of the smooth muscles of the bronchioles, intestine, uterus, and vascular system; dilatation and increased permeability of the capillaries of the skin and mucous membranes; stimulation of secretion in the lacrimal, nasal, pulmonary, and gastrointestinal glands; and production of pain or itching through the action of the end organs of pain nerves of the skin and mucous membranes. When administered in large doses, histamine shock develops. This shock is due in part to excessive capillary dilatation, allowing the escape of plasma from the circulation and resulting in a discrepancy between volume capacity of the circulatory system and the circulating blood volume.

In unanesthetized guinea pigs and rabbits, histamine, according to Dale and Laidlaw,[6] produces bronchoconstriction and death due to asphyxia. At post-mortem examination the lungs of the guinea pig are found in a condition similar to that seen in anaphylaxis, namely in a state of distention. The asphyxia is also due to a lesser degree to increased bronchial secretion plugging the smaller bronchioles. In the rabbit there occurs, as in anaphylaxis, due at least in part to bronchospasm and the ensuing respiratory difficulty and to pulmonary artery constriction, failure of the right side of the heart. In the cat and the dog, according to the above-mentioned authors, there is pulmonary hypertension due to pulmonary vasoconstriction. These authors[6] pointed out that small doses of histamine produce tachycardia in rabbits and cats. Their studies were made both in situ and on isolated organs, and they found that with larger doses of histamine there is a weakening of the heart. Went and Lissak[7] observed that in guinea pigs histamine produces increased amplitude of contraction, but the rhythm and rate of the heart beat are not affected. Andrus and Wilcox[8] stated that anaphylaxis and histamine produce constriction of the coronary arteries in guinea pigs and rabbits and an increase in coronary flow in cats. Cruikshank and Rau[9] agreed with the latter finding. Gunn[10] also reported that histamine causes diminution of the coronary outflow in the heart of the rabbit but increases the outflow from the coronary arteries of the cat. Essex and associates[11] stated that histamine brings about coronary vasodilatation in the dog. According to Anrep,[12] administration of the drug leads to coronary dilatation in the heart-lung preparation of man. Peters and Horton[13] injected histamine intravenously in man and found a loss of amplitude of the T wave leading to transient inversion, especially in I, III, and CR_2, indicating possible right ventricular strain. These findings agreed in part with those of Weiss and associates[14] who found that continuous infusions of histamine produce depression of all the complexes of the electrocardiogram, the effect being particularly marked on the T waves. The

T-wave changes occur simultaneously with acceleration of the rate and return to normal with return of the normal rate. These effects in the T wave in man are apparently not due to vagus influence for Hashimoto[15] could demonstrate no changes after administration of atropine.

OUTLINE OF EXPERIMENTS

The experiments were done on guinea pigs and rabbits and were divided into 2 parts. The Sanborn direct writing electrocardiograph was used, the standardization being adjusted to 15 mm. The limb electrodes consisted of small strips of copper which were wrapped about the extremities after they had been prepared by shaving and by the application of electrode paste. The precordial electrode was a miniature replica of the usual adult electrode, the base consisting of brass. Electrocardiograms were taken using standard leads I, II and III, and right and left chest leads (third interspace); they were taken immediately before and following histamine injection, and at intervals varying from 2 to 5 minutes thereafter until cardiac standstill or recovery occurred. The same technique was used on those animals which also received a protective dose of the antihistaminic drug.

Experiment I. Electrocardiographic Study Following Administration of Histamine in the Guinea Pig and Rabbit

A. Electrocardiographic Study Following Administration of Histamine in the Guinea Pig.—Six guinea pigs with an average weight of 350 Gm. were used. Histamine shock was produced by the intravenous injection of 0.4 mg. of histamine acid phosphate per kilogram of body weight. The histamine was administered in the dorsal vein of the penis. In 2 of the animals continuous tracings were taken as previously described. In all of the guinea pigs, the respirations ceased within 2 to 3 minutes after the histamine injection, the criterion used by Auer and Robinson[16] as the index of death. However, complete cardiac standstill usually did not occur until 10 to 80 minutes after the injection. The findings in the normal electrocardiogram of the guinea pig varied somewhat from those previously reported by Pratt.[34] There was some degree of variation in the P-R interval such as he had found, but the T wave was generally flat to upright in Lead I whereas he generally found it to be directed downward. The average normal rate (Fig. 1,*A*) was found to be 300 per minute, the P wave 0.02 second, the P-R interval 0.08 second, the QRS complex 0.03 second, and the Q-T interval 0.08 second. The electrocardiographic changes were practically the same for all animals, and we shall, therefore, tabulate the findings for only 1 animal in each experiment.

Forty-five seconds following the injection of histamine, the guinea pig showed the following changes: There was a complete atrioventricular block, and the T wave in Leads I and II which had been inverted in the normal tracing became upright. The next observed change (Fig. 1,*B*) occurred between 2½ and 3 minutes later. The T waves were high and peaked in Lead I and the left

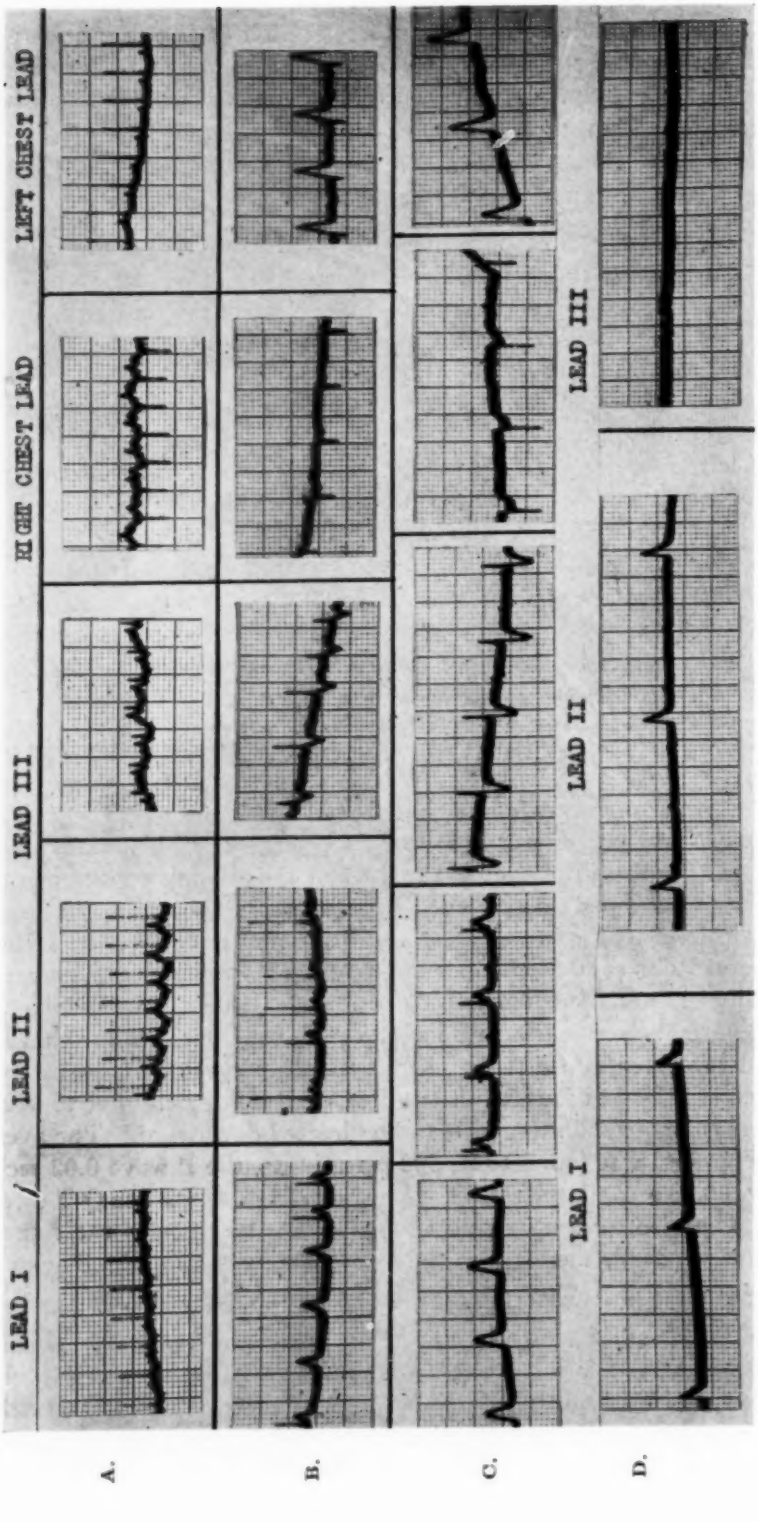

Fig. 1.—Effect of intravenous histamine on the electrocardiogram of the guinea pig. *A*, Control electrocardiogram before intravenous histamine. There is inversion of T in Leads I and II. *B*, After 3 minutes, there is a change to high T waves. There is also complete atrioventricular block and depression of ST in Lead III. *C*, Five minutes later the T waves are still higher; there is elevation of the ST segment in Lead II. *D*, Ten minutes later there is a 3:1 heart block followed by ventricular arrest in Lead III.

chest lead with inversion of T in III and the right chest lead. The Q-T interval was 0.11 second. There was variation in the amplitude of the QRS complex in Leads II and III, and complete heart block was present. Respirations ceased at the end of 3 minutes. By the end of a 5 minute period (Fig. 1,*C*), the T waves became increasingly taller, and there was elevation of the ST segment in Lead II and depression in Lead III. At 10 minutes (Fig. 1,*D*), there were varying degrees of heart block, i.e., 2:1 and 3:1, followed by ventricular asystole in Lead III.

B. Electrocardiographic Study of the Effect of Histamine on the Rabbit Heart.—Three rabbits with an average weight of 2,500 Gm. were used. Histamine shock was produced using the same dosage as in the guinea pig, the histamine acid phosphate being introduced in the marginal ear vein. The same procedure was used in taking the electrocardiograms as indicated previously. In the normal rabbit (Fig. 2,*A*) the heart rate varied between 165 and 200 per minute. The average P-R interval was 0.09 second, the QRS 0.03 second, and the Q-T interval 0.16 second. The T waves were usually upright. Twenty seconds after the intravenous injection of histamine (Fig. 2,*B*), the rate increased to 300 per minute, with an increase in amplitude of $R_{1,2}$ and a deep S_1. In Lead III there was auricular fibrillation and an occasional premature ventricular systole. The next change occurred at 2 minutes when the rate decreased to 100 per minute. The ST segments became depressed in Leads I and II and the left chest lead with flattening of the T wave in Leads I and II and the left chest lead. At 5 minutes (Fig. 2,*C*) there was a complete atrioventricular block in Leads I, II, and III with auricular fibrillation in the chest leads. Respirations had ceased at the end of 5 minutes. At 10 minutes (Fig. 2,*D*) the ST segments were elevated in Leads I and II and depressed in Lead III. There was a left bundle branch block present. In the period from 12 to 17 minutes, there was auricular fibrillation and paroxysmal tachycardia. At 17 minutes (Fig. 2,*E*) there was ventricular tachycardia with periods of ventricular arrest followed by ventricular arrest at 20 minutes.

Experiment II. Effect of Histamine on the Heart of Guinea Pigs and Rabbits When Administered Simultaneously With or Following an Antihistaminic Drug

Other workers[31] have found that with a dosage of 3 mg. per kilogram of Benadryl (β-dimethylaminoethyl benzhydryl ether hydrochloride) the amount of histamine base required to kill 100 per cent of the animals was 15 mg. per kilogram of body weight. It was thought interesting to determine whether or not electrocardiographic changes might occur upon injection of histamine when the animals were protected by the antihistaminic drug administered either prior to, or simultaneously with, the administration of histamine.

A. The Effect of Histamine When Preceded by the Administration of an Antihistaminic Drug.—One (2,500 Gm.) rabbit and 1 (300 Gm.) guinea pig were used for the experiment. The dose of histamine used was 0.4 mg. per kilogram of body weight. This was previously[32] found to be fatal in 100 per

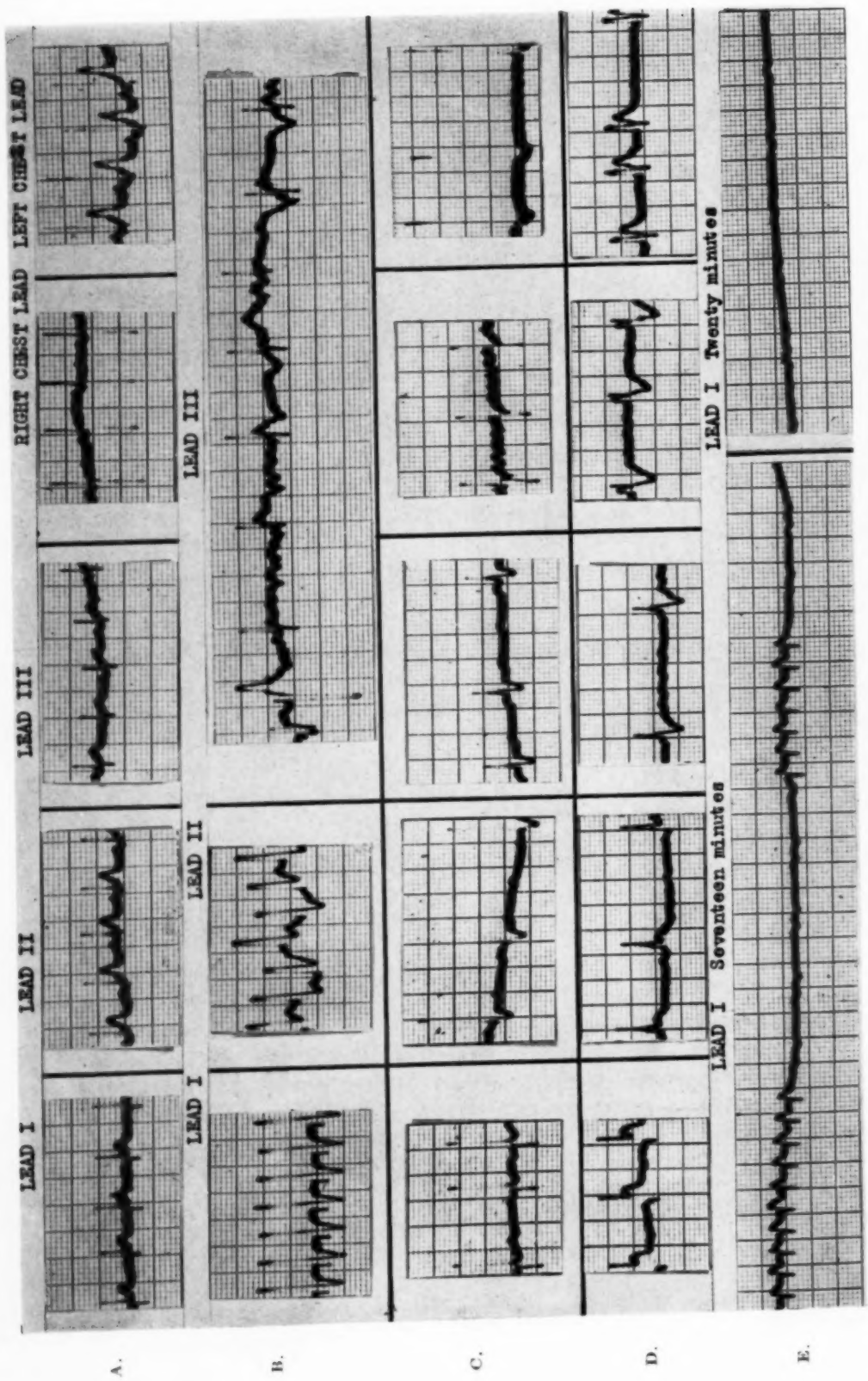

Fig. 2.—Effect of intravenous histamine on the electrocardiogram of the rabbit. *A*, Control electrocardiogram. *B*, Twenty seconds after intravenous histamine there is prolongation of QRS runs of paroxysmal tachycardia and auricular fibrillation. *C*, Five minutes after histamine there is auricular fibrillation and complete atrioventricular block. *D*, Ten minutes after histamine left bundle branch block is seen. *E*, Seventeen minutes after histamine there are periods of ventricular tachycardia and cardiac arrest; 20 minutes after histamine there is ventricular arrest.

cent of guinea pigs and was also found to be a lethal dose for rabbits. Benadryl was administered intraperitoneally in a dosage of 3 mg. per kilogram. Fifteen minutes later, the animals were given intravenous histamine in a dosage of 0.4 mg. per kilogram.

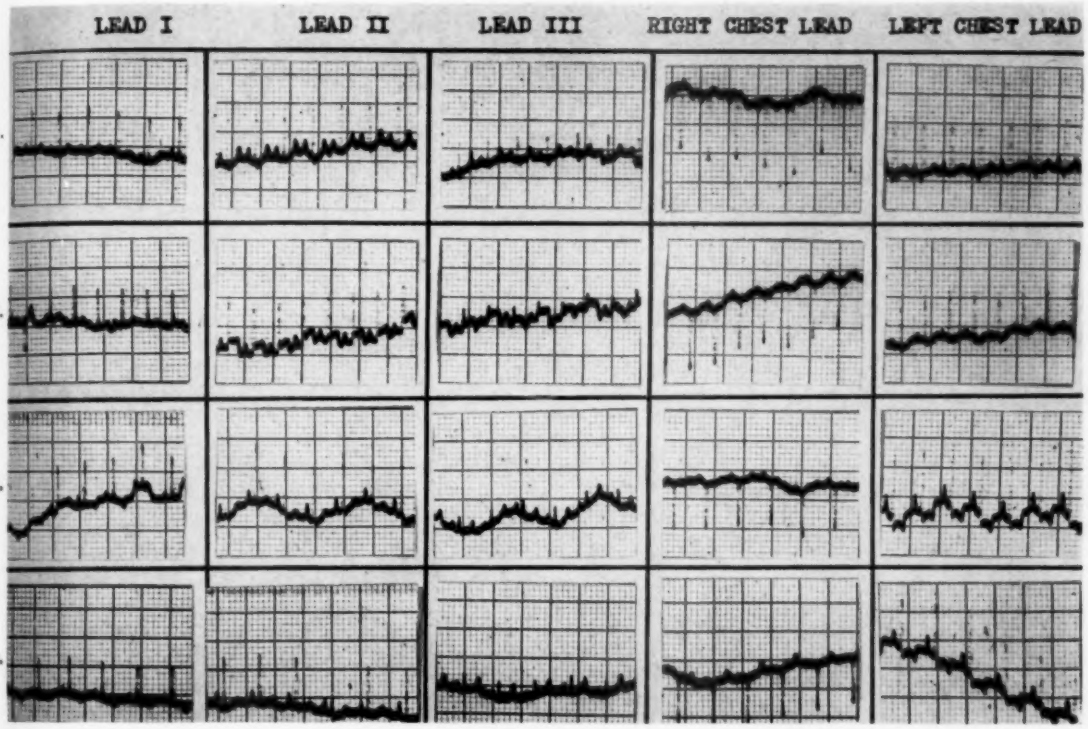

Fig. 3.—Effect of intravenous histamine on the electrocardiogram of the guinea pig following administration of Benadryl intraperitoneally. *A*, Control electrocardiogram before administration of histamine. *B*, One minute after histamine, there are elevation of ST in Lead I and premature ventricular systole in Lead I. *C*, Ten minutes after histamine, inversion of T in I and the left chest lead is seen. *D*, Thirty minutes after histamine, the T waves in Lead I and the left chest lead are still inverted.

The control electrocardiogram of the guinea pig (Fig. 3,*A*) showed a rate of 300 per minute with a P-R interval of 0.06 second, a QRS complex of 0.02 second, and a Q-T interval of 0.12 second. Note that all the T waves in the control tracing were upright except in the right chest lead. Immediately after the injection of histamine in the guinea pig, the animal manifested signs of mild histamine shock with difficult respirations, ruffled fur, and hyperirritability followed by a semistuporous state. One minute after the histamine injection (Fig. 3,*B*) the rate was 375 per minute with an elevation of the ST segment in Lead II and inversion of T_3 and depression of the ST segment in the left chest lead. There was an extrasystole in Lead I. At 2 minutes there was no essential change, and at 3 minutes the rate remained the same, but there was more inversion of T_3 and depression of the ST segment in the left chest lead. At 10 minutes (Fig. 3,*C*) the rate had returned to 300 per minute. In Lead I and the left chest

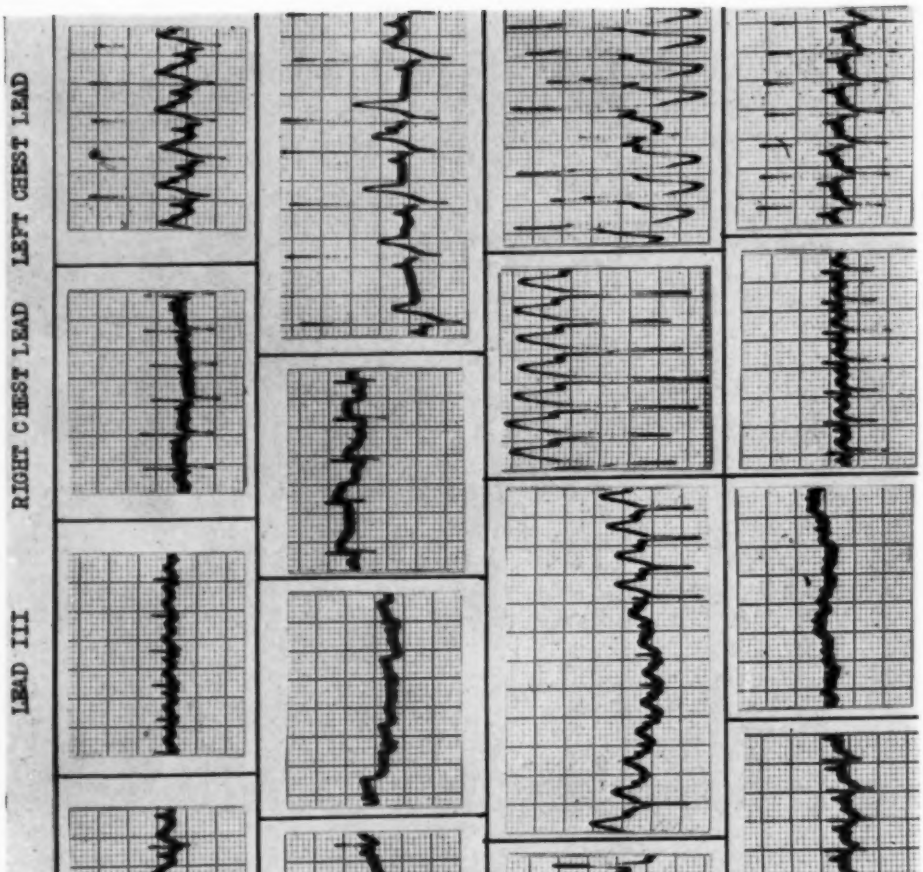

Fig. 4.—Effect of intravenous histamine on the electrocardiogram of the rabbit following administration of intraperitoneal Benadryl. *A*, Control electrocardiogram before histamine. *B*, Twenty seconds after intravenous histamine there are depression of ST in Leads I and II and the left chest lead and ST elevation in the right chest lead. *C*, Two minutes after intravenous histamine auricular paroxysmal tachycardia, nodal tachycardia (wandering pacemaker), and depression of ST segment in I, II and the left chest lead are seen. *D*, Five minutes after intravenous histamine there are nodal premature beats in I. The electrocardiograms at 30 and 60 minutes were normal.

lead, the T became negative, and there was slight depression of the ST segment in Lead II and the left chest lead. At 20 and 30 minutes (Fig. 3,*D*) the T in Lead I and the left chest lead was still inverted, and the rate was 250 per minute. The animal now appeared to be normal. At the end of 45 minutes T in Lead I was still inverted but appeared to be assuming the upright position in the left chest lead with still some sagging of the ST segment. At 70 minutes the T in Lead I and the left chest lead was upright, and the electrocardiogram had the same configuration as the control tracing (not shown due to limited space).

The control electrocardiogram of the rabbit (Fig. 4,*A*) showed a rate of 214 per minute, a P-R interval of 0.08 second, a QRS complex of 0.04 second, and a Q-T interval of 0.16 second. Twenty seconds after the injection of histamine, the animal manifested mild signs of histamine shock. The rate (Fig. 4,*B*) slowed to 125 per minute, and there was increased amplitude of the R in Lead III.

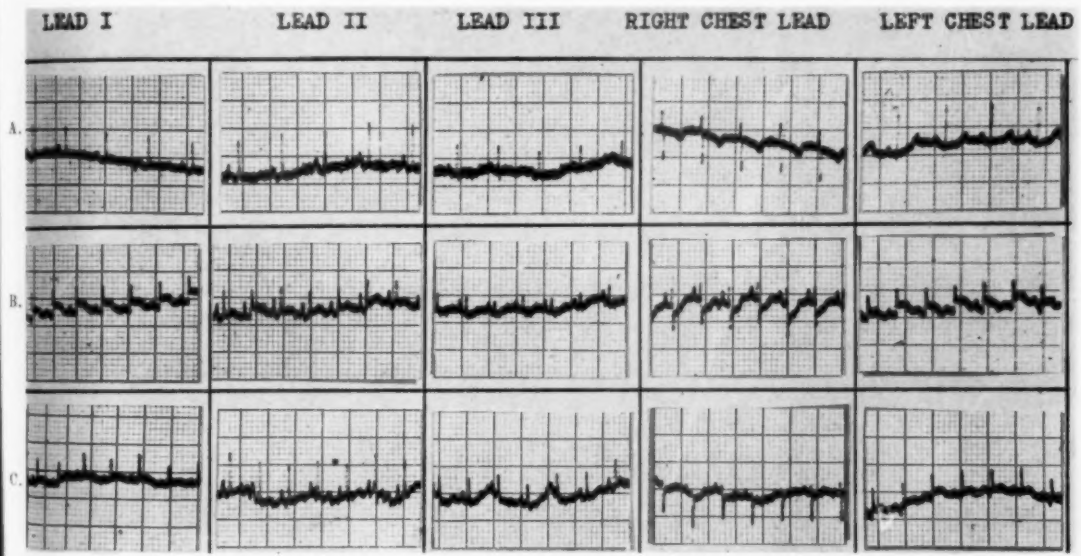

Fig. 5.—The effect of simultaneous administration of intravenous histamine and Benadryl on the electrocardiogram of the guinea pig. *A*, Control electrocardiogram. *B*, Five minutes after administration of the drugs there is ST elevation in Leads I and II and the left chest lead. *C*, Thirty minutes later there is still slight elevation of the ST segment in Leads I and II and the left chest lead.

There was depression of the ST segments in Leads I and II and the left chest lead and elevation of the ST segment in the right chest lead. At 2 minutes (Fig. 4,*C*) there was a paroxysmal auricular tachycardia, depression of the ST segments in Leads I and II and the left chest lead, and inversion of the T waves. At 5 minutes (Fig. 4,*D*) the rate was still rapid, but the ST segments and T waves were returning to normal. Note the nodal premature beats in Lead I. Electrocardiograms at 30 and 60 minutes were normal.

B. The Effect of Histamine When Administered Simultaneously With the Antihistaminic Drug.—In this experiment, histamine acid phosphate (0.4 mg. per kilogram) and Benadryl (3 mg. per kilogram) were given simultaneously

by the intravenous route in the dorsal vein of the penis of 1 guinea pig and the marginal ear vein of 1 rabbit. In the guinea pig, the control electrocardiogram (Fig. 5,*A*) showed a rate of 214 per minute, a P-R interval of 0.08 second, and a Q-T interval of 0.08 second; the T in Leads I, II, and III was flat. Fifteen seconds after the administration of the drugs, the guinea pig showed no signs of shock. The rate increased to 250 per minute. The ST segments were slightly elevated in Leads I and II, and the T in Leads I and II became upright. At 5 minutes (Fig. 5,*B*) the rate had increased to 300 per minute with an elevation of the ST segment in Leads I and II and the left chest lead with depression of the ST segment in the right chest lead. At 15 minutes there was no change, and at 30 minutes (Fig. 5,*C*) there was still slight elevation of the ST segment in Lead I and the left chest lead, with a persistent tachycardia. At 1 hour all the complexes were normal in appearance. Note the protection afforded by the Benadryl, the electrocardiographic findings consisting of a tachycardia and the transient changes in the ST segments.

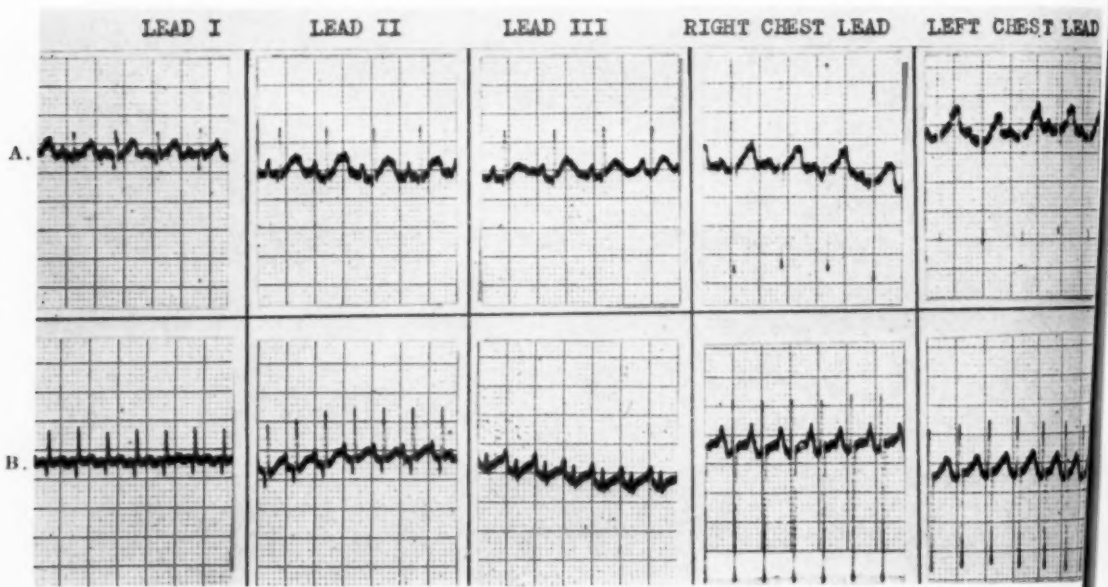

Fig. 6.—Effect of simultaneous administration of intravenous histamine and Benadryl on the electrocardiogram of the rabbit. *A*, Control electrocardiogram before administration of drugs. *B*, Five minutes after administration of drugs tachycardia and slight elevation of ST in I, II, and the left chest lead are seen. The electrocardiograms taken at 15 and 20 minutes were normal.

In the rabbit, the control electrocardiogram (Fig. 6,*A*) showed a rate of 187 per minute with a P-R interval of 0.08 second, and an S-T interval of 0.16 second. The T waves were all upright. After the administration of the 2 drugs, the animal manifested no signs of histamine shock. Five minutes after the injection (Fig. 6,*B*) the rate had increased to 300 per minute. There was slight elevation of the ST segments in Leads I and II and the left chest lead. There was increased amplitude of the R in Lead I and decreased amplitude of the R in Lead III

with some lowering of the T in Lead I. Electrocardiograms at 15, 20, and 60 minutes were normal. Note here again the protection afforded by the Benadryl with only minimal transient changes occurring.

MICROSCOPIC EXAMINATION OF THE MYOCARDIUM

Examination of the sections of the hearts of guinea pigs (Fig. 7) and rabbits following histamine shock showed no definite pathologic changes other than a few, small, scattered areas of focal hemorrhage which were felt to be due to the shock itself. Sections of the hearts of those animals protected by antihistaminics showed no pathologic changes.

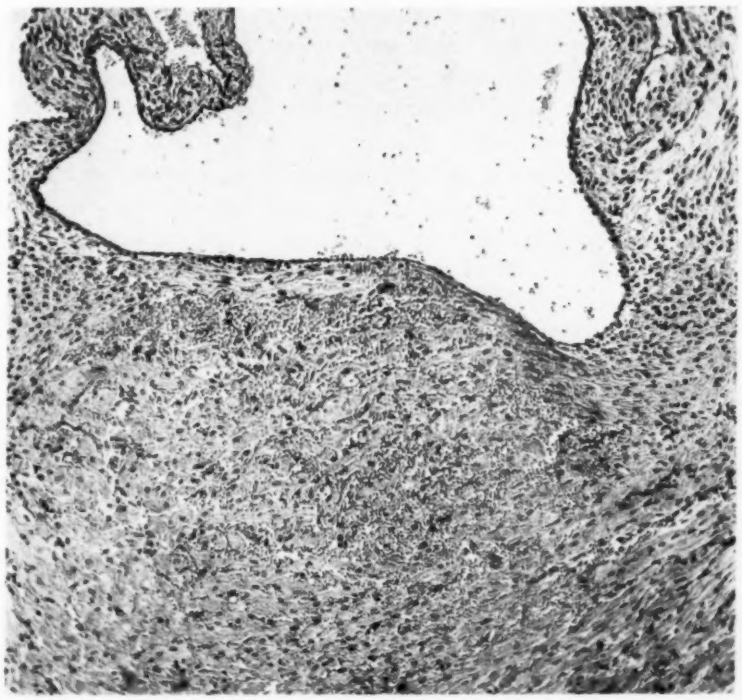

Fig. 7.—Section of guinea pig heart following histamine shock. There are some areas of focal hemorrhage due to the shock state.

DISCUSSION

The effect of injected histamine, it would appear, parallels for the most part the manifestations of anaphylaxis. Experimental observations[1,16,17] have established the fact that anaphylactic shock in animals is associated with severe typical and pronounced cardiac changes. These consist of variation in the frequency of the heart beat, disturbances in conduction (partial or complete heart block and bundle branch block), and signs of myocardial damage, especially changes in the T waves not unlike those seen in coronary artery involvement. The authors[1] have shown that these electrocardiographic changes in the guinea

pig and in the rabbit are identical with those produced by artificial asphyxia through ligation of the trachea. Greene and Gilbert,[18] in work with dogs, found practically no changes in the heart except a slight tachycardia and reduction in the P-R interval until failure of respirations. As anoxemia progresses, the T wave becomes increasingly more positive. Following respiratory failure, there are alterations in the rhythm of the heart, including conduction defects occurring as a result of the anoxemia. Wiggers[19] reported that in dogs a progressive decrease in the respired oxygen volume to 12 per cent increased the flow of blood by cardiac acceleration and redistribution of blood flow. He attributed the tachycardia to decreased vagal tone and possibly some direct effect on the sinoauricular node. With a further decline in the oxygen in the inspired air to 7 per cent, there develops an acute failure of the ventricles due to extreme anoxia. During this stage, various types of conduction and rhythm disturbances occur in addition to increased venous pressure, reduced pulse pressure, and decreased systolic pressure. Lewis and associates[20,21] concluded that these changes are independent of the action of the vagus nerves, for they occur in animals after they are given atropine as well as after section of the vagi. Resnick[22] noted a tendency of the ventricle to fibrillate after the establishment of the various grades of block that appear in advance stages of oxygen want. Cournand,[23] in a study of the effects of anoxia in man, indicated that it leads to pulmonary hypertension. He believed this to be due to the resulting stasis in the smaller pulmonary vessels and to increased capillary permeability and pulmonary arteriolar constriction. Anoxia in man produces definite changes in the electrocardiogram if coronary disease is present[24] and also in normal individuals under certain conditions. These latter changes, while varying in some respects, resemble those induced by histamine.[25] The various electrocardiographic changes from asphyxia are probably similar in other species and are independent of the cause of the asphyxia. There is some difference of opinion, however, as to whether allergic shock and bronchial asthma in man, which presumably are also associated with the liberation of a histamine-like substance and bronchoconstriction lead to pronounced changes in conduction. Castberg and Schwartz[25] reported 5 cases of allergic shock in man associated with flattening of the T waves in Leads I and II with depression of the ST segment in 3 cases, and increase in amplitude of P_2 and decreased amplitude of $R_{1\text{-}3}$. All changes which they encountered are in keeping with those found during experimental oxygen deficiency. They feel the changes were typical of anoxemia of the myocardium and attributable to decreased ventilation of the lungs. On the other hand, one of us in a survey[27] of fifty patients suffering from bronchial asthma found that minor transitory disturbances in cardiac conduction might occur during acute attacks of bronchial asthma, but that the asthmatic attacks do appear to have a permanent damaging effect upon the heart. Others[28,29] found that the asphyxial state produces a direct effect on the auriculoventricular mechanism of the heart, giving rise to delayed conduction of the normal cardiac impulse with progressively developing atrioventricular dissociation.

Our own present studies reveal that the electrocardiographic changes which occur during histamine shock in guinea pigs and rabbits are similar in

both species and also similar to those found in anaphylactic shock and artificial asphyxia. There is an analogy in the train of events: (1) variation in the heart rate, (2) disturbances in conduction, and (3) signs of myocardial involvement as demonstrated by various T-wave changes. It is not exactly clear as to how to interpret the latter changes in the T wave. It is reasonable to assume that they represent evidence of myocardial ischemia. This probably results in all species from the asphyxia, the coronary constriction, and the pulmonary hypertension associated with histamine shock. In addition, histamine shock is associated with an excessive dilatation and permeability of the capillaries, allowing escape of plasma from the circulation and thus resulting in a decrease in circulating blood volume. It is possible that this is also a factor in the production of myocardial anoxemia. These factors and particularly the pulmonary hypertension lead to right ventricular failure in the guinea pig, rabbit, cat, and dog when large doses of histamine are injected.[30]

There is considerable evidence to indicate that antihistaminics protect animals against fatal anaphylactic and against fatal histamine shock.[31,32,33] In our experiments, we found that in animals protected by the intraperitoneal injection of an antihistaminic agent, only slight electrocardiographic changes were present. In those animals in which the antihistaminic agent and histamine were administered simultaneously, the electrocardiographic changes consisted only of transient ST deviations. It is possible that the absorption by the peritoneal route was slow, accounting for the lessened protection and, therefore, the more pronounced changes in those animals, or that within 15 minutes all the drug had been absorbed and partially excreted, therefore not affording those animals as much protection. It appears also that the marked conduction defects seen in the unprotected animals were secondary to severe anoxemia and that the transient T-wave changes in the protected animals were probably due to mild temporary coronary insufficiency.

SUMMARY AND CONCLUSIONS

1. Electrocardiographic changes in guinea pigs and rabbits appear to be similar in artificial asphyxia, anaphylaxis, and histamine shock.

2. The changes in histamine shock consist of variation in the heart rate, conduction disturbances, and signs of myocardial damage.

3. The changes in the T waves in histamine shock are similar to those occurring in coronary artery involvement and suggest myocardial anoxemia.

4. Microscopic sections of the hearts of guinea pigs and rabbits during histamine shock showed no definite evidence of myocardial damage.

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THE ELECTROKYMOGRAM IN WOLFF-PARKINSON-WHITE SYNDROME

A Study of Left and Right Ventricular Ejection

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AMPLE evidence exists that in the Wolff-Parkinson-White syndrome[1] there is premature activation of the ventricles (ventricular pre-excitation), usually of the right ventricle but occasionally of the left.[2-6] This evidence is based on electrocardiographic studies of the potential effects produced by the two ventricles in extremity, precordial, esophageal, and intracardiac leads. There has been a great deal of disagreement, however, concerning the mechanical behavior of the ventricles, i.e., whether asynchronism in ventricular contraction results from ventricular pre-excitation.

The methods employed in the past for the detection of the presence or absence of ventricular asynchronism in this condition were based on studies of the events in the cardiac cycle during normal and aberrant conduction. The venous pulse was considered an indication of events in the right ventricle and the carotid pulse a reflection of the events in the left ventricle. These tracings were correlated with the electrocardiogram and phonocardiogram. The onset of the systolic rise of the carotid pulse represented the onset of left ventricular ejection, and the incisura represented closure of the aortic valve. In the venous pulse the onset of the "v" wave was considered to represent the closure of the pulmonic valve, giving clear indication of right ventricular diastole, but there was no clear-cut indication of the onset of right ventricular ejection since the "c" wave is probably produced not by right ventricular contraction but by the aortic impact against the superior vena cava. In a normal individual the rise of the "v" wave, the incisura of the arterial pulse, and the second heart sound are fairly synchronous. Delay in left ventricular ejection would be manifested by a delay in the rise of the carotid pulse and in the incisura as compared to the onset of the "v" wave of the jugular pulse. On the other hand, delay in right ventricular contraction, while not directly measured, would be suggested by a delay in the "v" wave as compared to the onset of the incisura of the arterial pulse. Furthermore, reduplication of the second heart sound, attributed to asynchronous closure of the semilunar valves, can be considered additional evidence of ventricular asynchronism.

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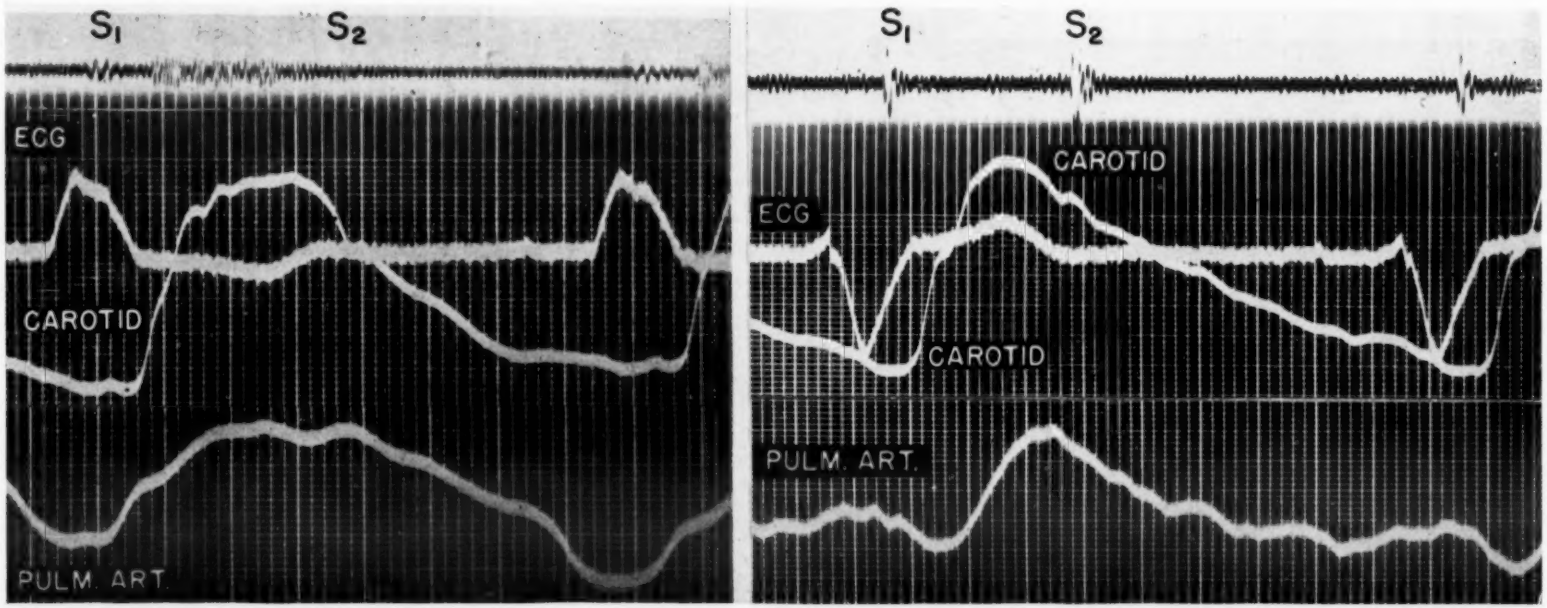
By employing such methods in the past the presence of asynchronism in ventricular contraction was demonstrated uniformly in bundle branch block.[8,9] However, uniform results were not obtained in Wolff-Parkinson-White syndrome. On the one hand, suggestive evidence of asynchronism (reduplicated second sound and delayed carotid pulse) was observed by several investigators,[5,10-13] while lack of asynchronism was reported by others.[14-17]

An attempt to obtain more precise comparison of left and right ventricular ejection was recently made by Richards and his co-workers,[18] who catheterized the right ventricle and pulmonary artery and obtained simultaneous recordings of intracardiac and peripheral arterial pressure and the electrocardiogram. They compared the onset of the rise in pressure of the right side of the heart with the rise in pressure in the brachial artery. In the one patient so studied they observed a delay in the onset of systole in both the left and right ventricles as compared to the measurements in normal individuals. They concluded that, although there was evidence of pre-excitation of the left ventricle through a left anomalous pathway (bundle of Kent), there was no mechanical asynchronism. This was attributed to the belief that the spread of the excitation wave was through the ventricular muscle at all times, so that both the left and right ventricular musculatures were activated before the normal impulse descending from the sinus node reached the ventricles, but the spread of the excitation was abnormal through both ventricles. In a later study of two patients by Ferrer and co-workers,[19] based on similar methods, ventricular asynchronism was detected in one and was absent in the other. This was attributed to differences in location of the terminus of the aberrant pathway, with resultant alteration of the sequence of ventricular depolarization and differences in the thickness of the two ventricles.

In electrokymography[20] there is now available a simple and accurate method of determining ventricular asynchronism from the onset of the aortic and pulmonary artery kymographic curves which indicate left and right ventricular ejection, respectively. In normal subjects slight asynchronism of ventricular contraction is frequently present. This was observed early in the slight disparity in the onset of the incisura of the carotid artery pulse and "v" wave of the jugular pulse. It was also proved experimentally by direct pressure readings from the left and right ventricles.[21] Electrokymographic studies have confirmed this physiological asynchronism.[22,23] Generally, the pulmonary artery curve slightly precedes the aortic curve by 0.01 to 0.02 second, but there may be a lag of 0.03 second in the two curves. Asynchronism of ventricular contraction can be reported only if the difference in onset of the aortic and pulmonary artery curve exceeds 0.03 second.

In our hands[24] and in those of others[22] electrokymography has clearly demonstrated the presence of ventricular asynchronism in bundle branch block (Fig. 1). Left bundle branch block is associated with delay in onset of the ejection phase in the aortic kymogram and right bundle branch block with delay in the ejection phase of the pulmonary artery kymogram. The duration of delay ranges from 0.04 to 0.06 second. It would be expected that if ventricular asynchronism were present in the Wolff-Parkinson-White syndrome, a similar lag between aortic and pulmonary artery ejection would be observed in the



A. B.

Fig. 1.—Typical bundle branch block. Pulmonary artery electrokymogram (lowest curve) recorded simultaneously with the phonocardiogram, electrocardiogram (Lead I), and carotid pulse tracing. Vertical time lines = 0.02 second. *A*, Left bundle branch block. The systolic rise of the pulmonary artery precedes that of the carotid pulse by 0.05 to 0.06 second, indicating that right ventricular ejection precedes left. *B*, Right bundle branch block. The systolic rise of the pulmonary artery follows that of the carotid pulse by 0.06 second, indicating that left ventricular ejection precedes right.

electrokymograms. In an attempt to throw further light on this disputed subject we have carried out detailed electrokymographic studies in four patients with Wolff-Parkinson-White syndrome with typical electrocardiographic features. The diagnosis was confirmed by intracardiac and esophageal electrocardiography carried out by Grishman, Kroop, and Steinberg.[25]

MATERIAL AND METHOD

Four patients with Wolff-Parkinson-White syndrome with typical electrocardiographic features were studied. Our method of recording and analysis has been described by us in previous reports.[23,24] By means of a four-channel apparatus* the electrokymogram was recorded simultaneously with the electrocardiogram, carotid pulse curve, and phonocardiogram. Kymographic curves were obtained from the ascending aorta and aortic knob, pulmonary artery, and left and right ventricular borders. The onset of the isometric and ejection phases of systole in the electrokymograms of each of these segments in relation to the other reference tracings was measured. The onset of the rise in the aortic and carotid pulse curves and pulmonary artery curve represented the onset of the ejection phase of the left and right ventricles, respectively. In previous studies it has been determined that there is a normal delay of 0.01 second in transmission of the pulse wave from the heart to the aortic knob and of 0.02 second in transmission to the carotid artery and through the recording mechanism for the carotid pulse. These physiological lags were taken into account in measuring the time of onset of left and right ventricular ejection from the aortic, carotid, and pulmonary artery curves. The onset of the isometric phase was more difficult to determine. Theoretically, the onset of the first heart sound represents the onset of the isometric phase of ventricular systole. This is true only if both ventricles contract simultaneously. However, as already stated, there may exist a physiological lag of 0.01 to 0.03 second between the onset of left and right ventricular systole. Therefore, the first major vibration of the first heart sound is produced by the isometric contraction of the leading ventricle. For this reason, the conclusions in this report have been based primarily on the analysis of the onset of the ejection phase in the two ventricles.

For detailed analysis of the electrokymographic curves the reader is referred to previous publications.[20,22-24,26-28] Generally speaking, upward movement of the curve indicates lateral or outward movement of the cardiac border, and in the case of the aorta or pulmonary artery it indicates expansion during ventricular ejection. Downward movement of the curve indicates medial or inward movement of the cardiac border, and in the case of the aorta or pulmonary artery it indicates arterial expansion during ventricular ejection. Downward movement of the curve indicates medial or inward movement of the cardiac border and in the case of the ventricular segment indicates contraction. The film speed in our records is 100 mm. per second, and the intervals between the vertical time lines represent 0.02 second.

*Manufactured by Cambridge Instrument Co., Inc., New York, N. Y.

ELECTROKYMOGRAPHIC FINDINGS

CASE 1.—The systolic rise of the aortic and pulmonary artery kymograms preceded that of the carotid artery by 0.01 second, excluding any significant asynchronism between left and right ventricular ejection. This was confirmed by analysis of the electrokymograms of the left and right ventricular borders, which indicated that the isometric phase began simultaneously in each ventricle, lasted for 0.03 second, and was followed by simultaneous inward movement in the ejection phase. The latter preceded the onset of the carotid pulse curve by 0.03 second in both the left and right ventricular curves.

CASE 2.—Comparison with the reference tracings indicated that the systolic rise of the pulmonary artery electrokymogram preceded that of the aortic knob by 0.02 second. This difference is within the normal range. Accurate comparison of the left and right ventricular electrokymograms could not be made because the curve from the right border was almost entirely auricular in character.

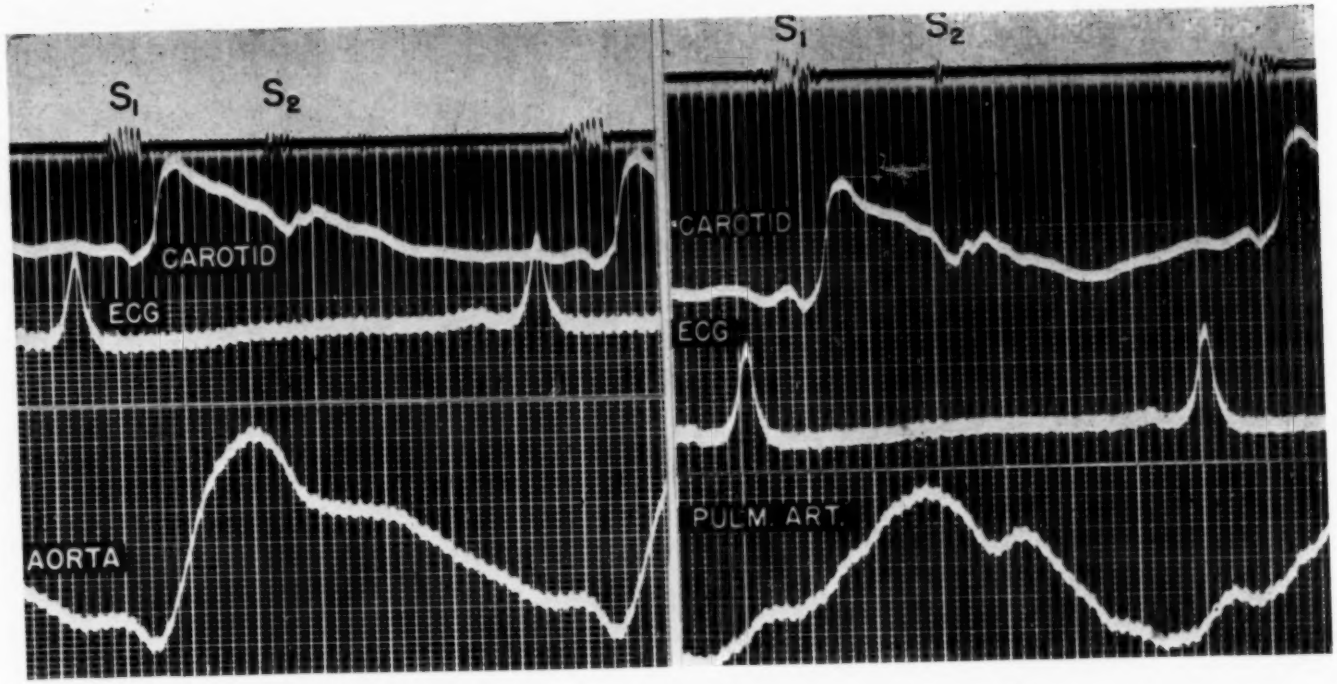
CASE 3.—The systolic rise of the aorta was synchronous with that of the carotid pulse curve (Fig. 2). This seems paradoxical but can be attributed to a positional change in the aorta at the onset of systole. Electrokymograms of the pulmonary artery from three different points in the posteroanterior and right oblique views disclosed that ejection began 0.01 to 0.03 second before the systolic rise of the carotid pulse curve. When corrected for the transmission time to the aortic knob, the findings indicated an interval of 0 to 0.02 second between left and right ventricular ejection, a difference which is within the range of normal. Although the use of ventricular border tracings to detect ventricular asynchronism is prone to error, owing to positional changes at the onset of systole, it is of interest that analysis of the left and right ventricular electrokymograms disclosed similar findings (Fig. 3). Comparison with other reference tracings suggested that the right ventricular systole preceded the left by 0.02 second.

CASE 4.—In the aortic electrokymogram the onset of the ejection phase was represented by a small, shallow serration beginning 0.02 second before the upstroke of the carotid pulse curve (Fig. 4). In the pulmonary artery electrokymogram there was a similar serration at the onset of the ejection phase which was sharper and vertical and preceded the carotid pulse curve by 0.02 second. The normal pulmonary artery-carotid pulse time relationship excludes any significant asynchronism in right and left ventricular ejection.

DISCUSSION

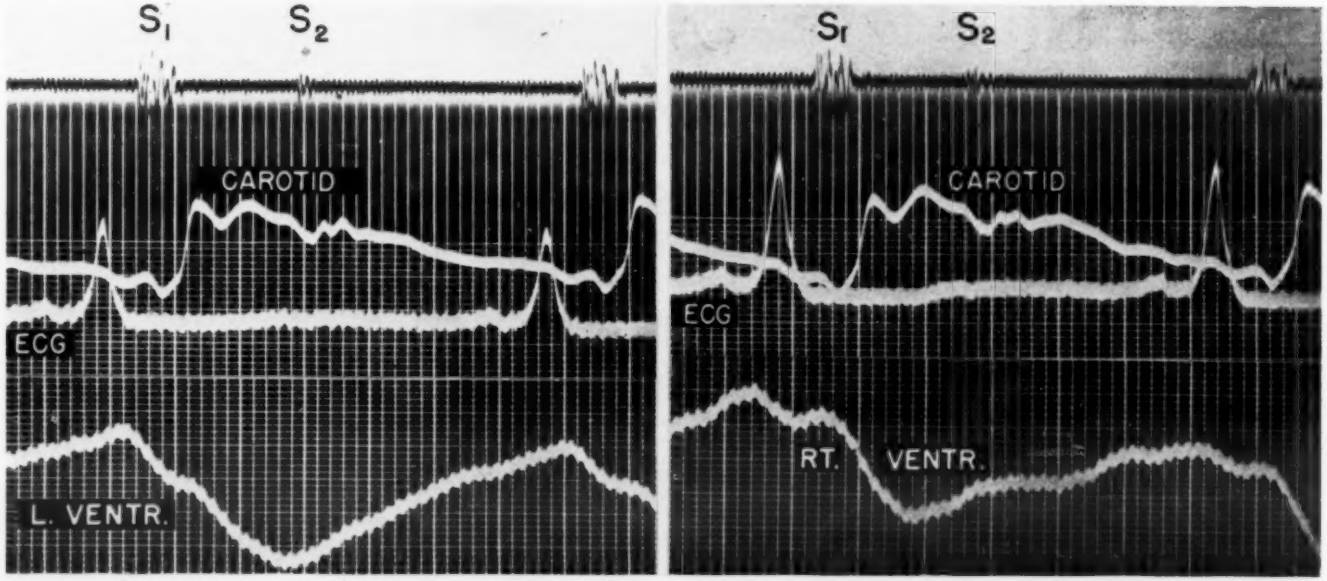
A review of the findings of our cases indicates that ejection from the left and right ventricles, as determined from the electrokymograms of the pulmonary artery and aortic knob, was simultaneous in two patients, while right ventricular ejection preceded left ventricular ejection by 0.02 second in the other two patients. These sequences of right and left ventricular ejection are within the physiological range of normal. The findings indicate a lack of significant asynchronism in left and right ventricular contraction. It is evident that the Wolff-Parkinson-White syndrome differs from bundle branch block in which mechanical asynchronism can generally be demonstrated by electrokymography as a significant lag in the onset of the aortic or pulmonary artery tracing, depending on whether left or right bundle branch block is present.

Although our series is admittedly a small one, the cases were well studied, and the kymographic findings were correlated with precordial, esophageal, and intracardiac electrocardiography which gave detailed information concerning the onset of right and left ventricular activation. It is probable, however, that in a larger series of cases evidence of ventricular asynchronism might be detected in some instances of Wolff-Parkinson-White syndrome.



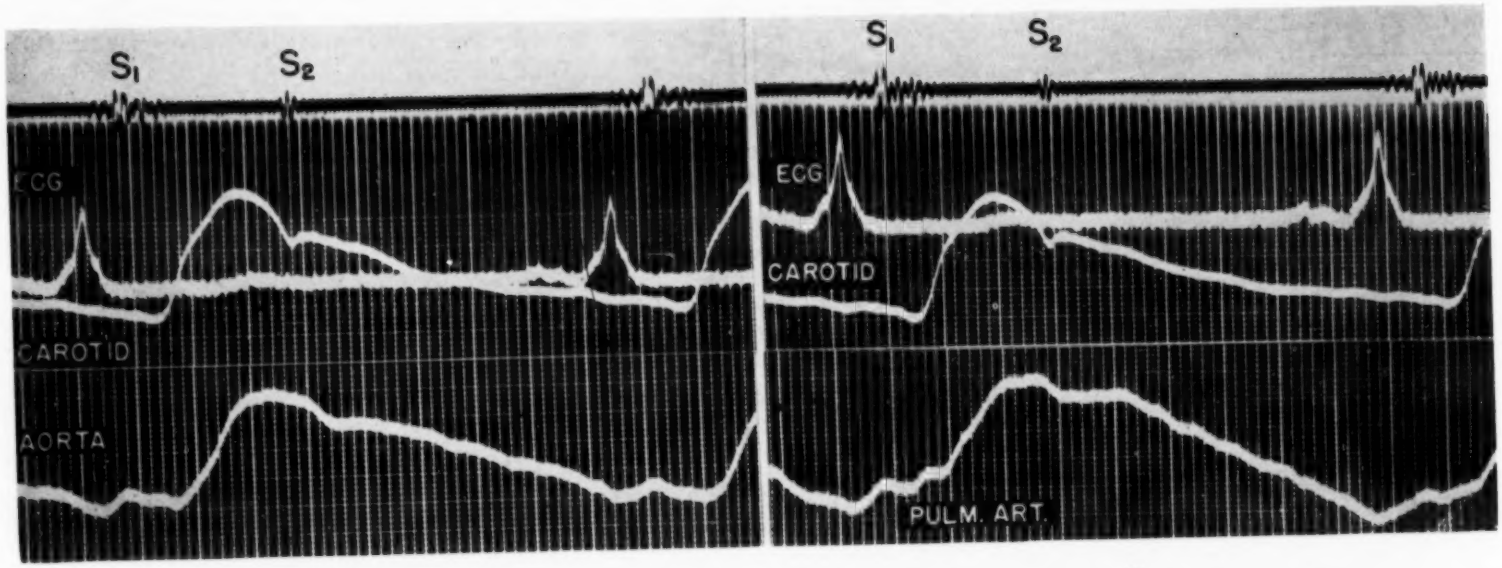
A. B.

Fig. 2 (Case 3).—Wolff-Parkinson-White syndrome. *A*, Aortic electrokymogram. The systolic rise of the aortic knob is synchronous with the systolic rise of the carotid pulse curve. *B*, Pulmonary artery electrokymogram. The systolic rise of the pulmonary artery precedes that of the carotid pulse by 0.02 or 0.03 second, a difference within the range of normal.



A. B.

Fig. 3 (Case 3).—Wolff-Parkinson-White syndrome. *A*, Electrokymogram of left ventricular border. The isometric phase is represented by downward movement synchronous with the onset of the first heart sound. The ejection phase begins 0.05 second later and is represented by a notch on this downward slope synchronous with the terminal vibrations of the first sound. *B*, Electrokymogram of right cardiac border. Right ventricular ejection is represented by a downward wave beginning 0.03 second after the onset of the first heart sound. Thus, right ventricular ejection precedes left by 0.02 second, a difference which is in the range of normal.



A. B.

Fig. 4 (Case 4).—Wolff-Parkinson-White syndrome. *A*, Aortic electrokymogram. The onset of ejection is represented by a small serration 0.02 second before the rise of the carotid pulse curve. *B*, Pulmonary artery electrokymogram. Ejection begins with a similar serration 0.02 second before the rise of the carotid pulse curve. There is no significant lag between pulmonary artery and aortic ejection.

Our analysis of left and right ventricular contraction is based primarily upon the findings in the aortic and pulmonary kymograms rather than on the movements of the left and right ventricular borders. The reason for this is that the electrokymogram is a complex curve which represents a composite movement of the heart border resulting not only from chamber filling and emptying but also from positional changes. The latter are the result of chamber displacement and torsion or tug of the heart and great vessels during contraction. Thus, it is possible that contraction of the left ventricle may induce movement of the right border by traction or tug. Therefore, premature contraction of the left ventricle might conceivably produce a simultaneous tugging movement of the right ventricular border, making it difficult or impossible to detect ventricular asynchronism from the ventricular kymograms. Another drawback to the ventricular kymogram as an indicator of ventricular asynchronism is the frequent difficulty of obtaining an undistorted right ventricular curve on the right border. The kymogram of the right border may be predominantly right auricular in character. For these reasons it has been found more accurate to employ the electrokymograms of the great vessels as indicators of ventricular ejection rather than those obtained from the ventricular borders.

The most widely accepted explanation of the peculiar electrocardiographic pattern in the Wolff-Parkinson-White syndrome is that first presented by Wolferth and Wood[3] and Holzmann and Scherf,[2] namely, that atrioventricular conduction occurs through an anomalous pathway connecting the auricle and ventricle on the right or left side. Anatomic evidence of such an anomalous pathway has been demonstrated by the historic work of Kent[29] and others.[30-32] Conduction through such an anomalous pathway, by short-circuiting the atrioventricular node and bundle, would be expected to result in premature excitation of one ventricle depending upon the location of the pathway. It appears paradoxical, therefore, that no asynchronism of ventricular contraction could be demonstrated in the electrokymograms studied. However, the presence of ventricular electrical pre-excitation, as suggested by the electrocardiogram, and the absence of asynchronous ventricular contraction, as suggested by the electrokymogram, can be reconciled by several possible explanations.

1. Assuming that the mechanism is premature activation of one ventricle through an anomalous atrioventricular pathway followed by normal activation of the contralateral ventricle by the normal impulse descending through the atrioventricular node and bundle, ventricular asynchronism would be expected but need not necessarily occur. Since the aberrant impulse travels directly through the ventricular muscle at a much slower rate than the normal impulse traveling through the His-Purkinje system, the premature excitation of the affected ventricle is offset by the slower rate of propagation of the aberrant impulse. Thus, mechanical response and contraction in both ventricles may occur simultaneously despite asynchronous activation.

2. A second explanation is based on recent observations of simultaneous pressure readings and electrocardiograms made during cardiac catheterization of two patients with this condition.[19] Asynchronous ventricular contraction was observed in one patient but was absent in the other. It was suggested that

during the anomalous conduction there was no conduction through the His bundle and Purkinje system in either ventricle. The aberrant impulse arriving via the accessory pathway on one side spread uniformly over both ventricles directly through the musculature. In such a concept, asynchronism might occur if the terminus of the aberrant pathway were situated eccentrically on one ventricular wall or if there were a great disparity in the muscle of the two ventricles. Asynchronism would be unlikely, however, if the terminus were near the interventricular septum and the impulse could spread simultaneously through both ventricular walls.

3. A third explanation is based on the analysis of the precordial, esophageal, and intracardiac electrocardiograms recorded on our four patients by Grishman, Kroop, and Steinberg.[25] In these electrocardiograms it was clearly demonstrated in all four patients that premature excitation occurred in both ventricles simultaneously. Furthermore, there was indication that intraventricular conduction in both ventricles proceeded from the epicardial surface to the endocardium, suggesting that the His-Purkinje system was not functioning and that aberrant pathways were functioning in both ventricles. Under these circumstances asynchronous contraction of the ventricles would not be expected.

SUMMARY

1. The electrokymogram was recorded in four patients whose electrocardiograms presented the pattern of the Wolff-Parkinson-White syndrome (short P-R interval and wide QRS complex). The findings were correlated with those observed in unipolar precordial, esophageal, and intracardiac electrocardiograms.

2. Electrokymograms of the aorta and pulmonary artery indicated that ejection from the two ventricles was simultaneous in two patients and that right ventricular ejection preceded left ventricular ejection by 0.02 second in the other two patients. The latter difference is within the normal physiological range. The findings indicate a lack of significant asynchronism in right and left ventricular contraction.

3. The possible explanations for the absence of mechanical ventricular asynchronism in the presence of electrical pre-excitation are presented.

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VARIOUS MECHANISMS IN RECIPROCAL RHYTHM

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RETROGRADE conduction in auriculoventricular rhythm (A-V nodal rhythm) leading to reciprocal rhythm is a rare condition. There is no doubt, however, that this condition is often mistaken for auricular or auriculoventricular extrasystoles and, consequently, is not diagnosed. In human beings, the phenomenon of reciprocal rhythm was first described by White,[1] who observed a curious bigeminy with sandwiching of an auricular complex between two ventricular complexes in a case of atrioventricular rhythm.

Earlier, in 1913, Mines,[2] in his classical experiments on frogs and rayfish, proved that after application of electrical stimuli to the heart, the auricle and ventricle could be made to beat alternately and a wave traveled from auricle to ventricle and then back again from ventricle to auricle. He called this condition reciprocating rhythm. Scherf and Shookhoff[3] were able to produce a similar disturbance of the rhythm experimentally in mammalian hearts. By cutting the vagus and then excluding the sinus node, an A-V nodal rhythm was established. After the induction of a series of ventricular extrasystoles, the last extrasystole which was conducted backward to the auricle frequently returned and again reached the ventricle. The phenomenon, which was termed "return extrasystole," they explained by the assumption of a longitudinal functional dissociation in the A-V connection.

Upon a review of the literature on reciprocal rhythm, Scherf[4] found that, in the majority of the clinical reports, only single reciprocal beats occurred; indeed, he found only one case (reported by Samojloff and Tschernoff[5]) which suggested, but did not prove, the possibility of a continuous reciprocal rhythm for a short period. Decherd and Ruskin,[6] in 1943, reviewed twenty-two cases in the literature and added three of their own. Since then, the cases reported by Naim,[7] Langendorf, Katz, and Simon,[8] Malinow and Langendorf,[9] Langendorf,[10] and Codina-Altés and Pijoan de Beristain[11] bring the total number in the literature up to thirty.

In the present paper, three cases of reciprocal rhythm will be reported. The first one shows an unusual form of intermittent tachycardia which, although its recognition was only possible after careful analysis, clearly illustrates the mechanism of reciprocal rhythm. The other two cases show some unusual features which, to our knowledge, have not previously been reported. In addition, a short tracing of another case which also shows some peculiarities will be given.

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CASE REPORTS

CASE 1.—The patient, whose electrocardiograms are presented, was a boy, 19 years old, who was followed in the Cardiac Clinic for more than five years prior to his death. During this time, he was suffering from a peculiar arrhythmia which was predominantly a bigeminal rhythm. The rhythm was interrupted by frequent attacks of paroxysmal tachycardia lasting from a few beats to several minutes. At times, the paroxysms lasted much longer, varying from a few minutes to several hours. In spite of those attacks, he was able to work in a factory for many years. The patient proved to have an unusual form of congenital heart disease known as Ebstein's disease and as such has been reported by Taussig.[12] The purpose of the present report is to analyze the arrhythmia.

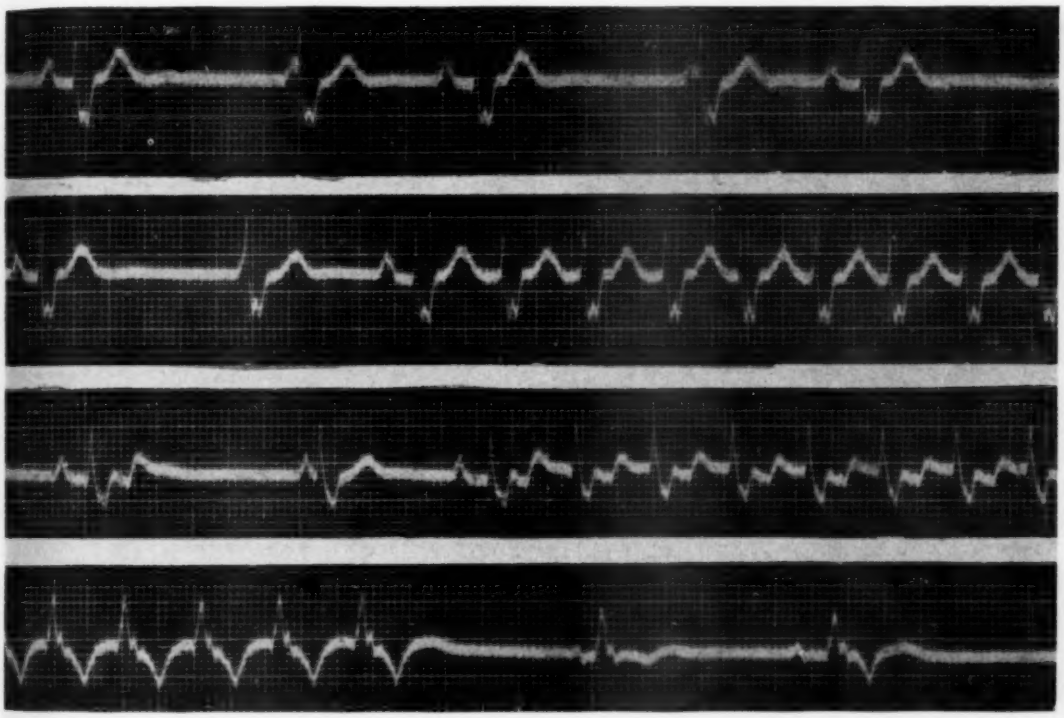


Fig. 1 (Case 1).—The upper two strips were taken in Lead I. The third strip represents Lead II and the last strip Lead III. Discussed in text.

The beginning of the tracing of Fig. 1 shows a slow arrhythmia characterized by alternation of a conducted and nonconducted P wave. Every other sinus beat was conducted to the ventricle with a P-R distance of 0.2 second. The QRS complexes showed signs of right bundle branch block. After each conducted beat, there was slowing of the sinus rhythm which resulted in functional dissociation only for one beat. However, there were two different types of ventricular complexes. Those which were preceded by P waves with a normal P-R interval were very bizarre: In Lead I, the beginning of the ST segment was isoelectric and went over with a sharp angulation into an upright and high T wave; in Lead II, the T waves were diphasic, and in Lead III they were unusually sharp, inverted, and deep. The escape beats showed a normal upright T wave in Leads I and II; in Lead III, the T waves were slightly inverted. The rate during the arrhythmic phase showed an average of 54 beats per minute. The bradycardia was interrupted by attacks of paroxysmal tachycardia. The cycle length during the paroxysm was 0.44 to 0.46 second, which corresponds to a rate of 132 beats per minute. The broad QRS complexes and the absence

of definitely visible P waves pointed to a paroxysmal ventricular tachycardia. However, the right bundle branch block during the bradycardia phase and the initiation of the attacks by a P wave strongly suggested that the tachycardia was of supraventricular origin in the presence of right bundle branch block.

The change between bradycardia and tachycardia as seen in Fig. 1 occurred in the majority of the tracings. The functional dissociation returned in every other beat during the bradycardia. In other instances, functional dissociation, due to different degrees of vagus stimulation, was present for two or three beats. This vagus effect appeared to end abruptly; thus, after two, or at most three, beats of functional dissociation, a normal sinus rhythm was restored (Fig. 2). This pattern repeated itself in an extraordinarily rhythmic form until it was interrupted by attacks of paroxysmal tachycardia of various durations.

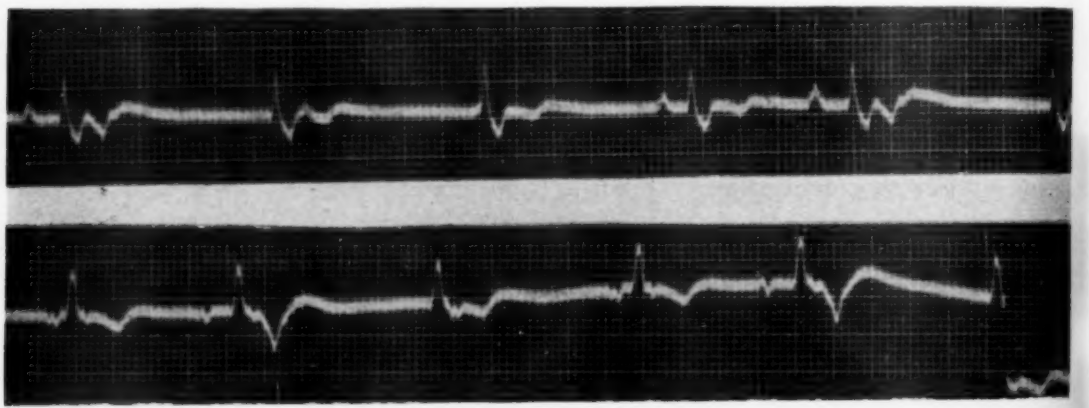


Fig. 2 (Case 1).—Between the sinus beats with the bizarre ST segments there is functional dissociation. The upper strip was taken in Lead II, the lower strip in Lead III.

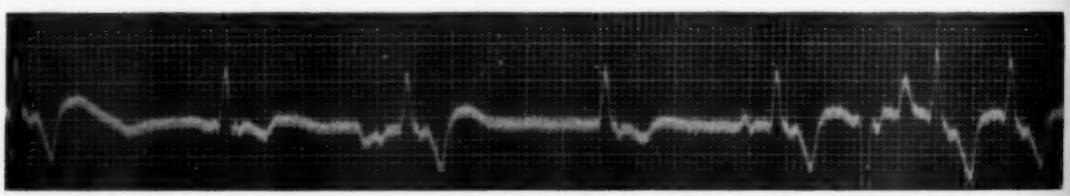


Fig. 3 (Case 1).—Lead III. Discussed in text.

The difficult feature in the interpretation was the apparent existence of two different types of ventricular complexes, both showing right bundle branch block. The ventricular complex during the paroxysm looked exactly like the conducted beat of the bradycardic phase and was different from the ventricular complex of the escape. The similarity of the ventricular beats with the bizarre ST segments suggested that the spread of the stimulus in those beats passed along the same path. This idea offered the clue to the real nature of the mechanism involved in this unusual arrhythmia. The bizarre shape of the ST segment could readily be explained by the existence of a hidden, inverted P wave.

The R-P distance was measured from the beginning of the R wave to the peak of the inverted P wave in all leads. This was necessary since it was not possible to measure the beginning of the inverted P wave in Lead III. The R-P distance was found to be 0.22 to 0.23 second throughout all records. These inverted P waves appeared to be caused by retrograde conduction of the stimulus from the ventricle to the auricle and to represent reciprocal auricular beats. The fixed time relation between the auricular contraction in which the P waves were inverted and the

preceding ventricular beat was strong evidence that re-entry from the ventricle to the auricle had taken place. The re-entrant waves were not transmitted back to the ventricles. In Fig. 1 during the bradycardic phase, those reciprocal beats occurred in every other beat, whereas in Fig. 2 they occurred in every third or fourth beat. During the tachycardia, the same ventricular complexes occurred, still containing the inverted P waves which indicated retrograde conduction. The R-P interval was exactly 0.23 second. This finding indicated the fixed coupling of auricular beats to preceding ventricular beats. During the slow phase, the retrograde conduction elicited a premature auricular beat, but the re-entrant wave was blocked at the A-V junction. During the paroxysm, however, the re-entrant wave was transmitted to the ventricle and from here again to the auricle, and so on. Thus, a continuous wave of excitation seemed to circulate between the auricle and the ventricle, producing a typical reciprocal rhythm.

There was a change in the type of the ventricular complex which was seen to occur repeatedly in the beginning of the paroxysm. This is illustrated in Fig. 3. The second beat of the paroxysm frequently had a different shape than the other beats of the tachycardia. The mechanism which produced this irregularity could be explained in the following way. The first beat was a sinus

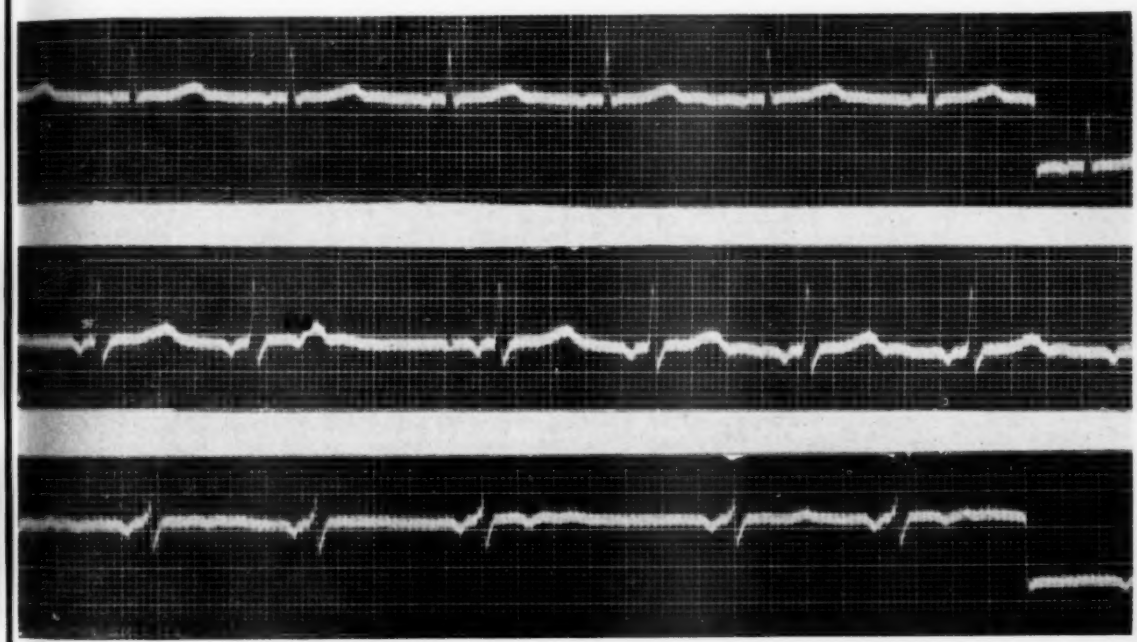


Fig. 4 (Case 2).—Upper A-V nodal rhythm or A-V nodal rhythm with first-degree A-V block. There are blocked premature auricular beats in Leads II and III.

beat with retrograde conduction just like the beat with the same configuration during the bradycardia. The following beat was a premature ventricular contraction which was conducted backward to the auricle. The sharp angulation before the start of the T wave was strongly suggestive of an inverted P wave. During the transmission of the impulse to the auricle, the excitation wave found a by-pass and was again transmitted to the ventricle. In simple words, the continuous reciprocal rhythm was not initiated by the sinus beat but by the second beat which represented a premature ventricular beat with retrograde conduction (Diagram L).

Summary.—This case illustrates a reciprocal rhythm which occurred within a sinus rhythm. There was a repeated alternation between a sinus bradycardia and a supraventricular tachycardia. During the bradycardia reciprocal auricular beats were followed by periods of functional A-V dissociation, whereas the periods of tachycardia represented continuous reciprocal rhythm.

CASE 2.—The patient, whose electrocardiograms are presented, was a girl, 15 years of age, who had suffered from rheumatic heart disease for the past four years. At the time the electrocardiograms were taken, the patient had clinical evidence of a subacute bacterial endocarditis; however, no autopsy was obtained.

An upper A-V nodal rhythm is illustrated in Fig. 4. The rate was 68 per minute. The P waves were slightly inverted in Lead I and deeply inverted in Leads II and III. The P-R interval was 0.13 to 0.14 second. In Lead II, after the second beat, there was an inverted P wave following the QRS complex after an interval of 0.28 second. This P wave represented a premature auricular beat and was followed by a noncompensatory pause but appeared to be blocked at the A-V junction. Another premature blocked auricular beat was seen in Lead III.

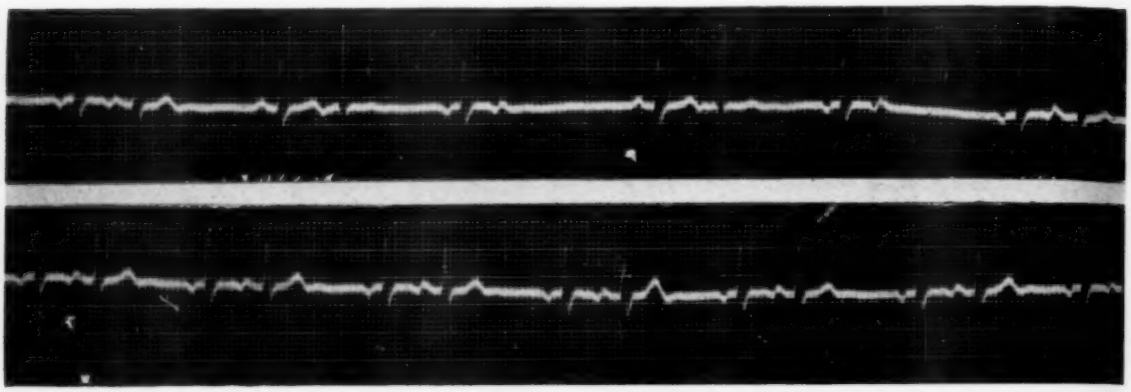


Fig. 5 (Case 2).—Reciprocal beats in an upper A-V nodal rhythm or in an A-V nodal rhythm with first-degree A-V block.

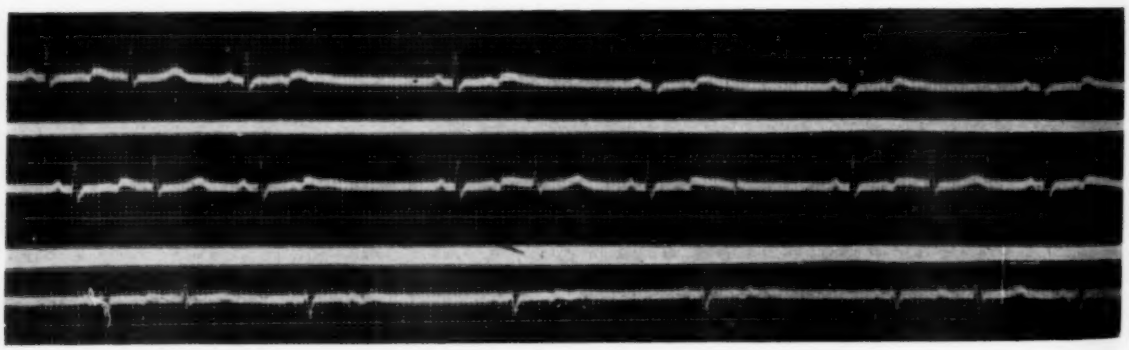


Fig. 6 (Case 2).—Sinus rhythm. Premature auricular beats, either blocked or conducted to the ventricle with prolonged conduction time, are seen throughout the entire record. The upper two rows represent Lead II, the lower row Lead III.

Frequently during the A-V nodal rhythm a bigeminal rhythm occurred. This was best seen in Lead II and illustrated in Fig. 5. The first beat of each group originated in the upper A-V node. The P-R was 0.12 to 0.14 second. It was followed after 0.44 second by a premature QRS complex. Between the two QRS complexes, there was an inverted P wave "sandwiched" between the ventricular complexes. The R-P distance was 0.27 to 0.28 second, and the following P-R interval was 0.16 second. In the fourth couple (lower row), the premature ventricular complex showed slight aberration and differed from the other complexes in that the QRS was wider and the T wave was higher. The premature beats were reciprocal beats. In the upper row, on two

occasions, the groups started with an upright P wave and a P-R interval of 0.17 second and an R-P interval of 0.30 second; the following P-R was 0.16 second. The next ventricular complex showed signs of aberration, the R wave was of higher amplitude than in the preceding ventricular complexes, and the T wave was almost isoelectric. Whereas the first two couples showed auricular and ventricular bigeminal rhythm, the third and fifth groups showed only auricular bigeminal rhythm due to blocked auricular premature beats. In this tracing, in two instances, a shift from A-V nodal rhythm to sinus rhythm was recorded, and in both instances the reciprocal beats persisted.

An electrocardiogram taken on the following day exhibits reciprocal rhythm during sinus rhythm (Fig. 6). The P-R interval was 0.17 second. The sinus beats were followed, after 0.30 second, by an inverted P wave, which was either blocked at times or at other times conducted to the ventricle with a P-R of 0.30 second.

Comment.—Most of the tracings showed a rhythm which, according to the old classical nomenclature, was fundamentally an upper A-V nodal rhythm. The P waves were diphasic, or slightly inverted, in Lead I and deeply inverted in Leads II and III. Some authors would call this pattern coronary sinus rhythm; although such a rhythm is not generally accepted, it should be considered in the presence of inverted P waves in Leads II and III and a P-R interval of more than 0.12 second. According to others,[13,14] this would be an A-V nodal rhythm with first-degree A-V block due to slight depression below the nodal pacemaker. From the A-V node, one impulse went up to the auricle and elicited an auricular contraction, and another one traveled down in antegrade direction and caused a ventricular contraction of such a nature that the antegrade conduction was slower or longer than retrograde conduction. Before the stimulus reached the ventricle, it found a by-pass and went up again and thereby produced a premature auricular contraction. The inversion of the P wave was proof of retrograde conduction. Before the stimulus reached the auricle, a reversal of the stimulus occurred again and, since it fell clear of the refractory period, it produced a ventricular response. Those premature beats were reciprocal beats and occurred in the form of bigeminy. On many occasions, the reciprocal auricular beat was blocked and not followed by ventricular response.

There was sinus rhythm throughout the entire record illustrated in Fig. 6. In the tracings the same type of premature beats as in Fig. 5 occurred in the form of auricular and ventricular bigeminy and, also, when there were blocked premature beats, as auricular bigeminy only. The similarity of this tracing to Fig. 5, especially the deeply inverted P waves, justifies the assumption that reciprocal mechanism also existed in this tracing.

The distance between the A-V nodal beats was invariably the same, regardless of whether the reciprocal beat was blocked (end of the upper strip, Figs. 4 and 5) or followed by ventricular response (Fig. 5). Since this interval was exactly the same, the assumption is justified that the course of the conduction was the same in both conditions and that the A-V nodal pacemaker had been discharged by a blocked reciprocal beat without affecting a ventricular contraction.[10,15] The block of the premature beat could be localized at or below the A-V node and not, as it might appear, at the upper A-V junction. This is best illustrated in Diagram G. During the sinus rhythm with reciprocal response (Fig. 6) it is possible, but not proved, that there was a similar discharge from the A-V node with blocked reciprocal beats (see Diagram M).

The assumption of a reciprocal mechanism in this case is based on the following facts: There was a dominant A-V nodal rhythm of the type in which the auricular contraction precedes the ventricular contraction. Each A-V nodal beat was followed by a premature contraction and thus caused a bigeminal rhythm. The P waves of the premature beats were almost identical in shape to the P waves of the A-V nodal beats (see Fig. 5). Those premature P waves were inverted and "sandwiched" between the QRS complexes. The similarity of the premature P waves to the P waves initiated by the A-V nodal beats indicated that the stimuli which elicited all these P waves must travel along similar retrograde pathways. Although inverted P waves are of common occurrence in auricular extrasystoles, it seems improbable that a P wave which arises from an auricular focus would show as deep an inversion as a P wave identical to that which originates from a deeper center. An A-V nodal extrasystole with first-degree A-V block can easily be ruled out. It would shift the A-V nodal rhythm in the same manner that a sinus extrasystole shifts the sinus rhythm. Thus, the postextrasystolic pause would correspond to the normal A-V nodal interval. Measurement, however, shows that the postextrasystolic interval was longer than the A-V nodal interval.

CASE 3.—The electrocardiograms were taken from a 5-year-old girl whose clinical diagnosis was situs inversus with levocardia and tetralogy of Fallot.

The first electrocardiogram was taken on Sept. 21, 1948. Fig. 7 taken in Lead I shows a group of four beats in quick succession, which were followed after a long pause by a single beat, and again, after a similar interval, the same group of four beats appeared. This picture repeated itself in a regular fashion. The first beat was an A-V nodal beat; the P wave was hardly visible but was contained in the QRS complex. The following quick beats consisted of two couplets due to reciprocal response. The R-P distance of the first bigeminy was 0.3 second; the R-P of the second bigeminy was 0.24 second. The following A-V nodal beat was not followed by a ventricular response; its P wave was present but hidden in the QRS complex. The last single beat at the end of the strip showed a P wave which followed 0.09 second after the QRS complex. The intervals between the A-V nodal beats measured as follows: 80, 116, 129, 176, 116, 126, 80, 116, and 126 per 100 seconds. The long intervals contained a reciprocal premature beat, whereas the short intervals did not show any ventricular response. The P-P distances were: 99, 112, 112, 99, 112, 112, 100, 112, and 112 per 100 seconds. Two consecutive P-P intervals were always equal in duration, measuring 112 per 100 seconds. The following P-P interval was shorter, because it did not contain a reciprocal beat. The reciprocal stimulus, which traveled from the place of the reversal down to the ventricle, discharged the A-V node before reaching the ventricle. This discharge shifted the A-V nodal rhythm and was responsible for the longer P-P interval containing the reciprocal beat, but the longer intervals were not present when the retrograde P wave was not followed by a ventricular response since there was no discharge of the A-V node by a reciprocal impulse. The gradual decrease of the R-P distance might lead one to assume that there was improvement of the retrograde conduction. This assumption can be contradicted by the fact that two consecutive P-P intervals were invariably equal in duration, thus proving that the time for retrograde conduction remained constant during this period and that the variation of the R-P intervals could be explained only by variation in forward conduction to the ventricle. Delay in antegrade conduction will shorten the R-P interval, and reversely, acceleration of antegrade conduction will lengthen the R-P interval.[4]

The configuration of this tracing, which repeated itself with almost mathematical accuracy, appeared to be completely clear. It was due to the reciprocal beats and their effects on the sequential beats. The diagram under the tracing (Fig. 7) illustrates this rather clearly. Beat 1 was not followed by a reciprocal response, therefore no second stimulus traveled down the bundle, and the next A-V nodal beat found a more rested bundle and antegrade conduction was easy

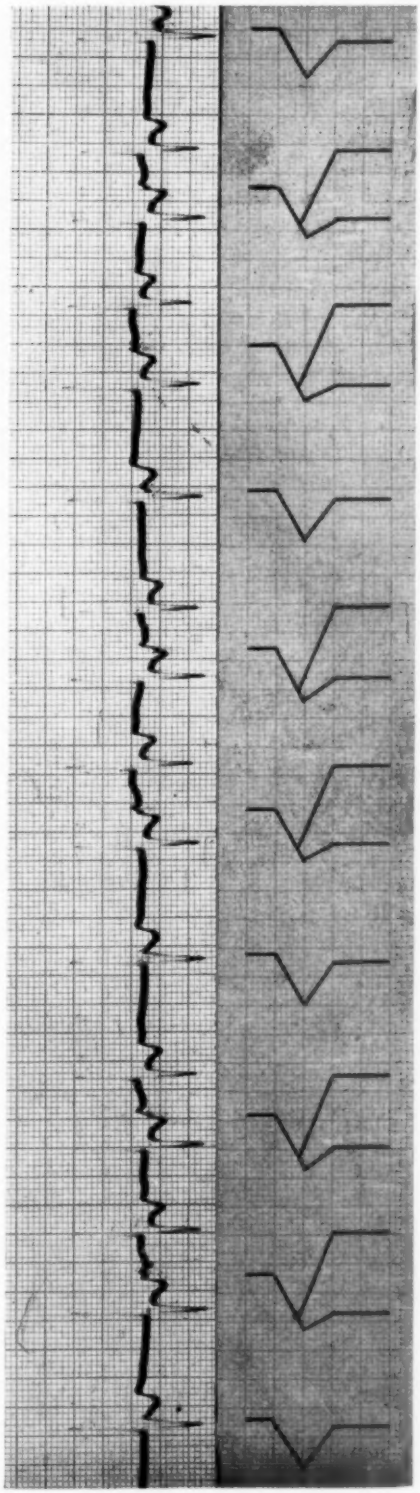


Fig. 7 (Case 3).—Allorhythmia due to reciprocal beats and their effect on forward conduction of the sequential beats.

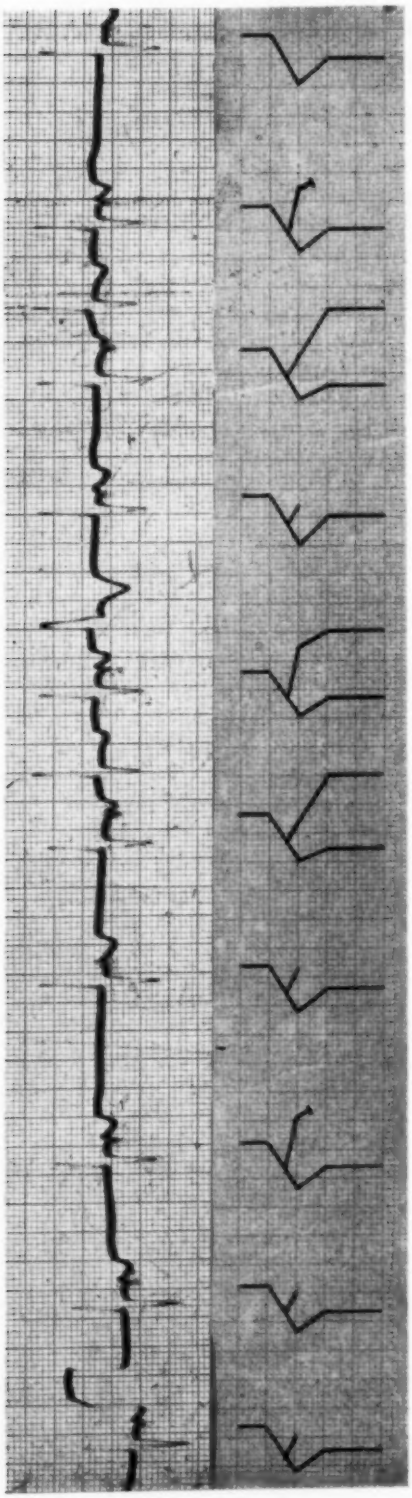


Fig. 8 (Case 3).—Delay of conduction in the course of the reciprocal pathway. Discharge of the nodal pacemaker by blocked reciprocal beats. Discussed in text.

and quick. This was manifested by a long R-P. The third nodal beat showed delayed forward conduction, since the bundle had not yet recovered from the preceding reciprocal ventricular beat, and this delayed forward conduction resulted in shorter R-P distance. The following reciprocal response slowed the downward conduction of the sequential A-V nodal beat even more, and R-P became very short or P was within the QRS complex. The last beat was not followed by a reciprocal beat and gave the bundle time to recover; then the same mechanism started again.

The exact time and place of the reversal of the reciprocal impulse is not known, but the time of the nodal discharge by the reciprocal stimulus can be calculated easily from the difference of the P-P interval which contained a reciprocal beat and the P-P interval without a reciprocal response. The latter represents the length of the undisturbed A-V nodal period and measured 0.99 second. The difference was 0.12 to 0.13 second. The reciprocal beat shifted the A-V nodal rhythm only for 0.13 second. After 0.13 second of the primary nodal discharge, the A-V node was discharged again by the reciprocal impulse. The R-P distance was 0.3 second in the first beat and 0.24 second in the second beat. Since the R-P interval corresponds to the retrograde conduction time from the A-V node to the auricle less the antegrade conduction time from the A-V node to the ventricle, the actual retrograde conduction time must be longer than 0.3 second. If the nodal discharge occurred as early as 0.13 second after the primary A-V nodal discharge, the conclusion may be valid that the reversal took place in the early part of the retrograde pathway and relatively long before the inscription of the inverted P wave.

Fig. 8 again shows Lead I taken on the following day. The same two features as in Fig. 7 were constantly present; namely, reciprocal rhythm and variation in R-P due to variation in antegrade conduction. But there are a few other peculiarities which were not seen in the previous record.

At first glance the rhythm appears to be very irregular. On more exact analysis, however, it is found that there was fundamentally a rather regular atrioventricular rhythm which was disturbed after every third A-V nodal beat by a mechanism which, to our knowledge, has not been reported and which was responsible for this peculiar allorhythmia. The heart was completely under the control of the A-V node. P waves were inverted, which is unusual in Lead I, and followed the ventricular beats with gradual shortening of reversed conduction. The first four beats showed an R-P of 18, 18, 18, and 13 per 100 seconds; the following R-P intervals measured: 24, 18, 14; 25, 18, and 14 per 100 seconds. The intervals between the R waves of the A-V nodal beats were rather irregular and measured 95, 96, 124; 96, 106, 126; 91, 106, and 120 per 100 seconds. The P-P intervals, however, showed some regularity, as in Fig. 7, and measured 100, 100, 123; 103, 101, 122; 100, 100, and 121 per 100 seconds. Two consecutive P-P intervals were always identical in length; the following P-P interval was longer.

The fifth beat was followed by a premature ventricular contraction. Between the QRS complexes was an inverted P wave which characterized this bigeminal group as due to reciprocal rhythm. The following bigeminy was also caused by reciprocal conduction and showed aberrant conduction, a common occurrence in reciprocal beats. The first four beats in the beginning of the tracing and the seventh and ninth A-V nodal beats were not followed by reciprocal responses, but the P-P distance which followed these beats in question, was identical in duration to the P-P interval which contained a reciprocal beat. This proves the occurrence of blocked reciprocal beats in those nodal beats which were not followed by visible reciprocal ventricular response (Diagram J). The reciprocal impulse traveled down and discharged the A-V node and was blocked at or below the A-V node.[10] Localization of the block can be assumed by its effect on the sequential beat. Blocking of the impulse just before reaching the ventricle may cause slowing in antegrade conduction of the next beat, since the bundle has not yet recovered and also the R-P of the next beat will be shorter (third beat and the second beat from the end of the strip in Fig. 8). Block at the A-V nodal pacemaker or just below does not affect the bundle; consequently, the next beat is conducted more quickly in antegrade direction. This is manifested by a longer R-P interval (Diagram J).

As it was mentioned before, there was, on many occasions in this record, after every third A-V nodal beat, a prolongation of the P-P interval for just one beat. Two sequential auricular intervals measured 100 per 100 seconds; the following interval, however, was 122 per 100 seconds. The explanation we have to offer for this peculiar behavior is that the prolongation of the P-P

interval was caused by a disturbance of conduction within the reciprocal pathway. There seemed to be a delay in downward conduction between the place of the reversal and the A-V node, resulting in a late discharge of the A-V node. The delay in discharge can be measured by the difference between the longer and the shorter P-P distances, which amounted to 0.22 second. The late nodal discharge, due to delayed reciprocal conduction, could also be caused by blocked reciprocal beats (Fig. 8).

Although the time of this delay can be determined easily, the mechanism leading to this late discharge does not seem to be completely clear. Two possibilities should be considered. As in other conduction disturbances, the conduction tissue, after conducting a few reciprocal beats, becomes fatigued, with the result that the next downward impulse is delayed. This resulting delayed A-V nodal discharge shifts the rhythm and gives the reciprocal pathway time to recover; consequently, the next reciprocal impulse travels downward in its usual time. Since it reaches the A-V node at a time when the subnodal tissue is still refractory, it is blocked after discharging the A-V node and not followed by a ventricular response. The other possibility (as shown by the dotted line in Diagram J) is that the reciprocal stimulus is conducted downward in its normal time but reaches the A-V node at a time when the bundle is in a refractory state. Nevertheless, the stimulus remains effective at the A-V node until the subnodal tissue recovers. In that case, the delay would be within the A-V node and would be caused by the prolongation of the recovery period for forward conduction.

The variation in R-P intervals was explained by variation in antegrade conduction. Analysis of more than 100 beats revealed the following relations between R-P intervals and the sequential beats.

A. R-P intervals of from 0.24 to 0.30 second were followed by reciprocation. From the difference between the P-P intervals containing a reciprocal beat and the P-P intervals without a reciprocal beat it was calculated that the reciprocal stimulus discharged the A-V node 0.12 to 0.13 second after the primary nodal discharge (Diagram I). Therefore, the refractory period of the A-V node must be a little less than 0.12 second.

B. R-P intervals of 0.18 to 0.19 second were followed by reciprocal beats with delayed downward conduction to the A-V node (Diagram J).

C. R-P intervals of from 0.13 to 0.18 second were not followed by ventricular response, but the analysis revealed nodal discharge by blocked reciprocal beats (Diagram J and Fig. 8).

D. R-P intervals of less than 0.13 second were not followed by any reciprocal conduction (Diagram I and Fig. 7).

Groups B and C demonstrate instances of concealed A-V nodal conduction.[10] Failure to recognize this concealed conduction may lead to errors if one should attempt to determine the refractory period of the node and the bundle. The absolute refractory period is usually determined by the shortest R-P interval which is followed by a reciprocal beat and the longest R-P interval which is not followed by reciprocation. Between these two measurements lies the refractory period. In group C with an R-P of 0.13 to 0.18 second no ventricular response was seen; consequently, one would assume that the refractory period was longer than 0.18 second. However, there is evidence that the nodal pacemaker was discharged by a blocked reciprocal beat before the appearance of the auricular inscription.

Fig. 9 shows a tracing taken on the same day. There was a slight tachycardia due to reciprocal beats. The primary A-V nodal rhythm had a rate of about 55 per minute, but every nodal beat was followed by an interpolated reciprocal beat which brought about a slight tachycardia with a rate of 110 beats per minute. Indeed, those beats were interpolated since they did not disturb the fundamental A-V nodal rhythm. The inverted P waves were hidden in the T waves but still visible. In the lower strip, P waves were not visible at all, but otherwise the configuration of the beats was the same as in the upper tracing, particularly, the groups of bigeminy were clearly seen. This justifies one to assume that re-entry took place above the A-V node without exciting an auricular contraction (Diagram B). This mechanism, occurring in a single group, was previously described by Cutts.[16] It has, however, never been observed as occurring in succession or during a tachycardia.

After digitalization, the following changes were observed: A-V nodal rhythm became slower and R-P much longer. Reciprocal rhythm was continuously present. Occasionally, the "sand-

wiched" P waves became upright. Electrocardiograms, taken two months later, showed no remarkable changes, but four months later, an A-V nodal rhythm was present, which showed only occasional reciprocal response.

Summary.—There were typical reciprocal beats in an A-V nodal rhythm. Three features, hitherto not observed in human beings, were encountered: (1) variation in antegrade conduction as effect of reciprocal beats on subsequent beats, (2) conduction disturbance in the course of the reciprocal pathway leading to a late discharge of the A-V node, and (3) tachycardia caused by interpolated reciprocal beats without auricular excitation.

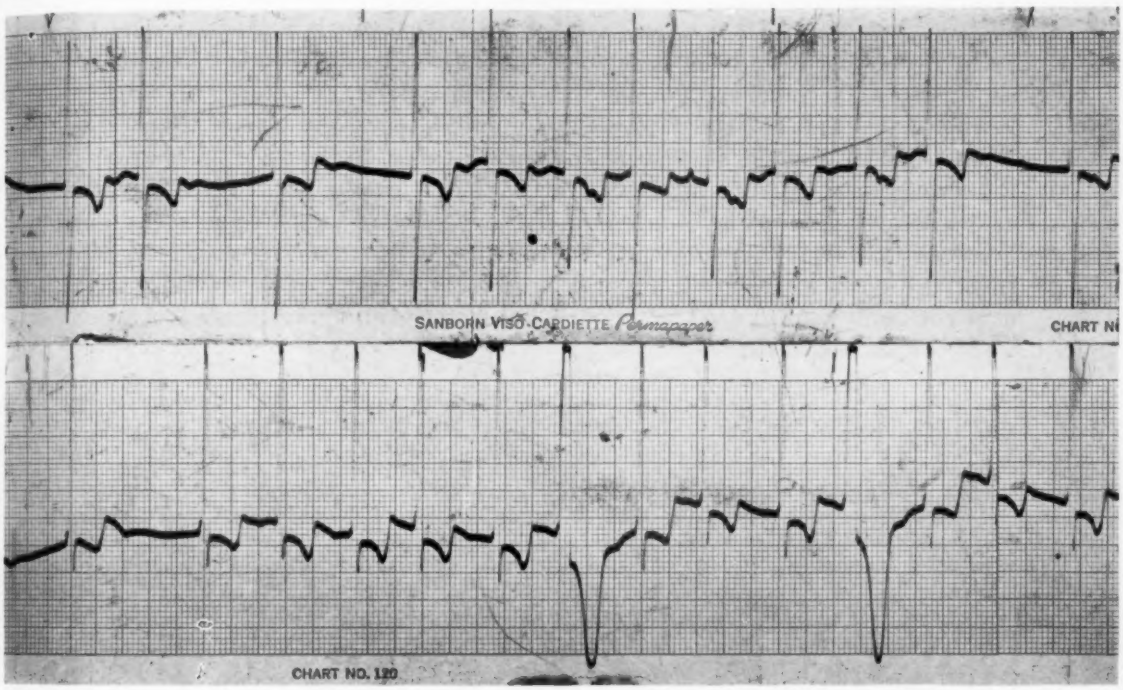


Fig. 9 (Case 3).—The upper tracing (V_5) starts with an A-V nodal beat followed by a reciprocal beat. The inverted P wave is well seen within the inverted T wave. The fourth ventricular beat initiates a slight tachycardia with a rate of 110. The first, third, fifth, and seventh beats of the paroxysm are followed by an inverted P wave. The other beats are slightly premature and not followed by P waves. Those premature beats are reciprocal beats. The tachycardia is caused by the reciprocal beats, but it does not represent a continuous reciprocal rhythm. The lower strip (V_3) shows a similar mechanism. The tachycardia is composed of bigeminy, but no inverted P waves are seen. The first beat of each couple is an A-V nodal beat; the following beat is a reciprocal beat. The A-V nodal beat is probably conducted backward, and the stimulus re-entered above the A-V node without exciting the auricle. On two occasions aberration of the reciprocal beat was seen (Diagram B).

DISCUSSION

These three cases which have been described and analyzed in detail display, as the most prominent feature, the phenomenon of reciprocal rhythm. This pattern can easily be recognized if one follows the description of White of inverted P waves sandwiched by two ventricular complexes. This has been demonstrated in Cases 2 and 3, as well as in almost all reported cases. The

sandwiching of the inverted P wave, therefore, is of practical importance in the recognition of reciprocal rhythm. However, it does not constitute the conditio sine qua non in the diagnosis of reciprocal rhythm. An instance of absence of the sandwich pattern is shown in Fig. 9 and Diagram B. Occasional fusion between a retrograde impulse of a premature ventricular beat and a sinus beat was reported by Langendorf, Katz, and Simon.[8] This fusion changed the contour of the inverted P wave, rendering it isoelectric or slightly positive.

Reciprocal beats are best diagnosed in Lead II. In Lead I, the retrograde P wave is usually isoelectric or slightly diphasic. Case 3 showed definitely inverted P waves in Lead I, which is unusual. The reported case was diagnosed as situs inversus with levocardia. According to Taussig,[12] this condition is usually associated with an extremely complicated malformation of the heart, which probably could account for this unusual retrograde conduction pattern. Normally, in Lead III, the T waves are often diphasic. An inverted retrograde P wave may cause similar changes on the T waves, so that the recognition of the retrograde conduction in Lead III may be easily overlooked. If the inversion of the P wave falls on the top of an inverted T wave (Case 1), one sees a deeply inverted T, similar to a coronary T wave, a condition we might call negative superposition of a retrograde P on an inverted T wave. In questionable cases, it might be of help to use the unipolar right arm lead, in which a retrograde P wave is usually upright.

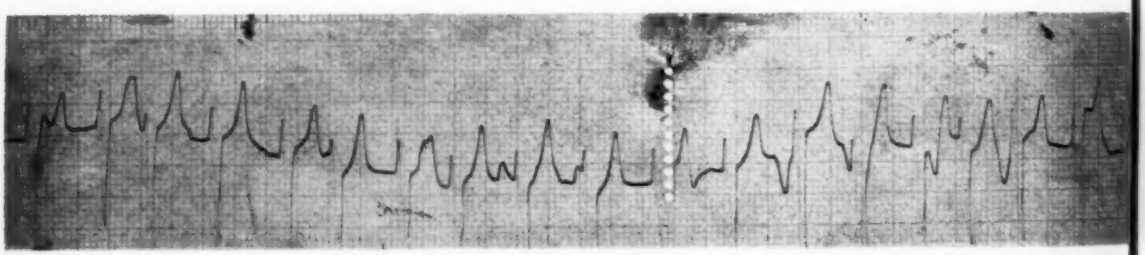


Fig. 10.—Pseudoreciprocal and reciprocal rhythm. Discussed in text.

White,[1] in his first description, called this picture a very curious type of bigeminy. This pattern becomes even more curious if reciprocal rhythm is associated with variation in retrograde or antegrade conduction. In Drury's case of tachycardia, the two prominent features were retrograde block and reciprocal rhythm.[17] P waves appeared progressively later in relation to the ventricular complexes, owing to retrograde block. Reciprocal beats appeared when R-P intervals were gradually lengthened (Diagram C). Similar cases were reported by Blumgart and Gargill.[18] Katz and Kaplan[19] described a case exhibiting both reciprocal and pseudoreciprocal rhythm during interference dissociation. In our Case 3, a very curious allorhythmia, i.e., arrhythmia occurring in a rhythmic fashion, was brought about by reciprocal beats, which caused slowing in antegrade conduction of the sequential beats.

Scherf[3,4] was able to produce reciprocal beats in his animal experiments which occurred as couplets or triplets. This was also seen by Decherd and Ruskin[6]

in human beings. Fig. 10 shows a nodal tachycardia with a triplet due probably to reciprocation. This electrocardiogram was taken from a patient with tricuspid atresia during the Blalock-Taussig operation. The first one-half of the tracing shows interference dissociation between a sinus and an A-V nodal rhythm. Upright P waves were seen following the QRS complexes. The premature beats were pseudoreciprocal beats showing capture of the ventricle by the preceding P wave. After the third pseudoreciprocal beat, a normal P wave was seen which was conducted to the ventricle; the next P wave appeared slightly before the ventricular beat. Following this part, upright P waves were not seen until just before the end of the strip. During this period of nonvisible sinus activity, an A-V nodal rhythm with progressively increasing retrograde conduction was present. After the inverted P wave which followed the QRS complex, two premature ventricular beats appeared which represented two sequential reciprocal beats.

Arrhythmia of various types is known to occur during anesthesia and operation. Ziegler,[20] in his extensive study on electrocardiographic changes during anesthesia and operation, reported displacement of the normal pacemaker in 88 out of 175 cases submitted to the Blalock-Taussig operation and in twenty other cases of cardiac surgery. Nineteen per cent of this group showed classical A-V nodal rhythm with inverted P waves before or after the QRS complexes. In his paper (Fig. 2,*C*), a premature QRS complex was seen on two occasions following a retrograde conducted P wave. Those premature beats were undoubtedly reciprocal beats. With this high incidence of A-V nodal rhythm, it should not be surprising to see this phenomenon more frequently during operation.

Aside from showing the rare phenomenon of reciprocal beats, our cases display a few peculiar features. In Case 1, there was a change between a sinus bradycardia and a supraventricular tachycardia (Diagram K). During the bradycardic phase, the beats, which were identified as due to reciprocal conduction, were always followed by functional dissociation for one to three beats. The course of the reciprocal beats was from auricle to the ventricle and again back to the auricle. The re-entrant wave was not transmitted to the ventricle. Together with those blocked premature auricular beats, some vagus hypertonicity came into play, causing transition of the sinus rhythm to A-V nodal rhythm with functional dissociation. It seems to be of interest that during the bradycardic phase two conduction disturbances of opposite nature could be observed, namely, reciprocal retrograde conduction, causing auricular contraction, and retrograde conduction block of the following escape beat, which gives rise to functional dissociation.

During the tachycardia, the re-entrant wave was transmitted to the ventricle and from here again to the auricle, causing a real continuous wave of excitation between the auricle and the ventricle (Diagrams K and L). This is a definite case of continuous reciprocal rhythm which confirms the assumption of Mines[2] that a mechanism of similar nature produced by him in animals might give rise to paroxysmal tachycardia in human beings.

There are only two analogous cases of sinus rhythm reported in the literature, the cases of Naim[7] and of Codina-Altés and Pijoan de Beristain,[11] in which continuous reciprocal rhythm persisted for some time, causing paroxysmal tachycardia.

Case 2 probably showed reciprocal beats in an upper A-V nodal rhythm or in an A-V nodal rhythm with first-degree block, i.e., this type is one in which auricular contraction preceded ventricular contraction. There was a change between upper A-V nodal rhythm and sinus rhythm with the persistence of reciprocal beats during both rhythms. Discharge of the A-V nodal pacemaker by blocked reciprocal beats without affecting a ventricular response[10] can be demonstrated in this case (Diagram G).

Case 3 was characterized by a peculiar allorhythmia due to reciprocal beats and their effect on subsequent beats (Diagram I). There were two couplets representing reciprocal beats alternating with an A-V nodal beat not followed by reciprocation. The reciprocal ventricular complex had the same effect on the following A-V nodal beat as an interpolated extrasystole on a following sinus beat; this effect caused a slowing in antegrade conduction which was manifested in the tracing by progressively decreasing R-P intervals. The second reciprocal beat had such a slowing effect on antegrade conduction of the next A-V nodal beat that R-P became very short or zero and no reciprocation was possible.

Variation of the R-P interval is common in reciprocal rhythm and is usually explained by variation in retrograde conduction, which ordinarily is associated with irregularity of the P-P interval. Therefore, it has been assumed that constancy of P-P intervals excludes reciprocal rhythm. The case under discussion, however, showed reciprocal rhythm with decreasing R-P intervals due to variation in antegrade conduction in the presence of constant retrograde conduction, as evidenced by constant P-P intervals. Only Scherf,[4] in his animal experiments, reported the effect of interpolated return extrasystoles on sequential beats, but no case has been reported in human beings. Rather similar to our Case 3 is the case of Ziesler,[21] which was interpreted as being a case of sinus arrhythmia with interference and dissociation.[22] In our opinion, his patient demonstrated the same mechanism as our patient.

Case 3 also showed some other unusual features whi h are illustrated in Diagrams B and J and explained in the discussion of the diagrams.

In a review of the literature in 1943, Decherd and Ruskin[6] reported that reciprocal rhythm occurred only in A-V nodal rhythm. The often quoted case of McMillan and Wolferth[24] represented an exception in which occasional reciprocation was present in a high-grade 2:1 S-A block. This case, as well as the cases of Naim[7] and of Codina-Altés and Pijoan de Beristain[11] and our two cases, give evidence that reciprocal rhythm may also occur in a rhythm which originates in the sinus node or upper A-V node. The course of the pathway in these patients is the reverse to that seen in A-V nodal rhythm, namely, from auricle to ventricle and back again to the auricle. The pathway of the returning stimulus is not exactly known. Three theories have been put forward to explain this unusual disturbance of conduction. Mines[2] postulated that different fibers of the junctional tissue would recover at slightly different rates and that, according to the recovery process, the impulse would pass from the auricle to the ventricle in one group of fibers and in reverse direction in another group. Scherf[3,4] has been able to demonstrate the existence of longitudinal functional dissociation, at least above the A-V nodal pacemaker. This has been con-

firmed by Korth and Schrumpf.[25] Decherd and Ruskin proposed the concept that, above the A-V node, there exists an area of refractory tissue of varying size and shape in which varying stages of recovery may exist through which conduction will take place in varying directions and at varying rates. Common to all these theories is the concept that one group of fibers conducts the impulse upward and another group conducts them downward.

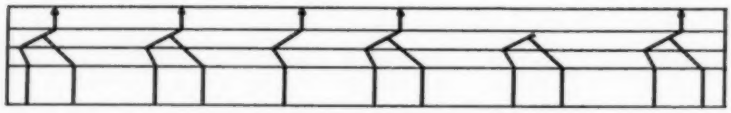
In order to discuss various types of reciprocal conduction encountered both in the literature and in our own cases, diagrams are shown which illustrate the mechanism involved in this condition.

Diagram A shows ventricular bigeminy which is due to reciprocal beats. This seems to be the most common type and was first described by White.[1,26] The stimulus originates in the A-V node. Within one bigeminal group, there is one stimulus with retrograde and two stimuli with antegrade conduction, and the bundle is stimulated twice. The relation between R-P and P-R is either fixed or the duration of the P-R varies with that of the preceding R-P. The more brief the R-P is, the longer the P-R.[4] Aberration of the reciprocal beat is common in couples with short R-P intervals.[27] If R-P is very short, no reciprocation will occur. Bigeminal rhythm may occur throughout the whole record or only as a single event. Occasionally patients with upright P waves who seem to belong to this group have been reported. Since nodal rhythm with upright P waves has been described, the possibility cannot be excluded that many cases of nodal rhythm, complicated by ventricular bigeminy, might be caused by reciprocal conduction. In this connection, it seems to be of interest that Perelman and Miller,[28] after a thorough search of the literature, found eight different types of mechanisms which may result in A-V nodal bigeminy.

In the fifth couplet, there is no P wave visible between the ventricular complexes. This points to the fact that the retrograde impulse re-entered, without exciting the auricle, above the nodal tissue.[15] The diagnosis can only be made when other groups show inverted P waves, but this possibility should be considered even without visible P waves within one bigeminal group.

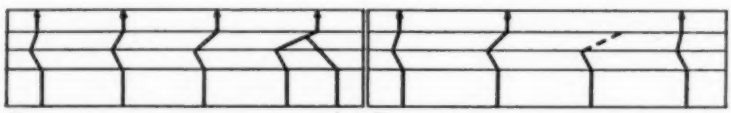
The place of the reversal of the reciprocal stimulus is not known exactly. It might vary from patient to patient and might occur anywhere within the retrograde pathway from the A-V node to the auricle. However, if one can measure the normal A-V nodal interval, the time of the nodal discharge by the returning stimulus can easily be calculated. This might give us some clue as to the part of the retrograde pathway on which the reversal might occur. In our Case 3 (Fig. 7 and Diagram I), it was calculated from the difference of the A-V nodal interval, which contained a reciprocal beat, and the normal A-V interval that the nodal discharge by the returning impulse took place 0.12 second after the primary nodal discharge. The R-P interval was 0.3 second. This indicates that the discharge of the nodal pacemaker by the reciprocal stimulus occurred relatively long before the auricular inscription and that the reversal must have taken place in the early part of the retrograde pathway.

The returning stimulus in Diagram A discharges the A-V node and shifts the A-V nodal rhythn. In Diagram B, however, the reciprocal beats are inter-



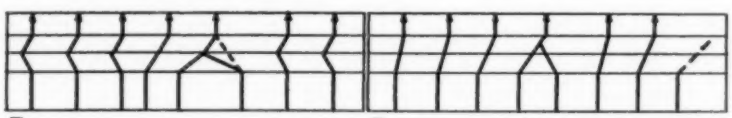
A A-V nodal rhythm with ventricular bigeminy. Common type.

B A-V nodal rhythm with reciprocal beats causing tachycardia. At the end of the strip reciprocal beating without eliciting auricular contraction.



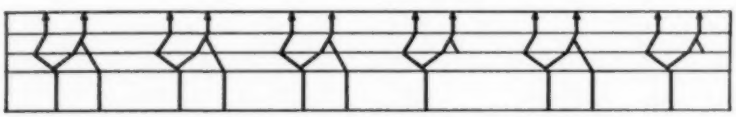
C A-V nodal rhythm with increasing retrograde conduction and reciprocal beat following the last A-V nodal beat.

D Progressively increasing retrograde conduction and block.



E Return-extrasystole of Scherf.

F Ventricular paroxysmal tachycardia with retrograde conduction, reciprocal beat and retrograde block.



G A-V nodal rhythm with first degree A-V block and reciprocal beats. Auricular and ventricular bigeminy.

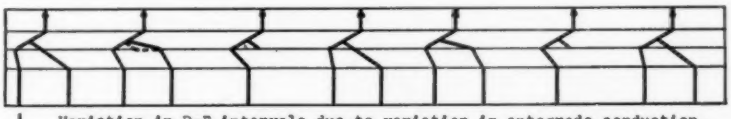
H Reciprocal beats and discharge of the nodal pacemaker by a blocked reciprocal beat in the fifth complex.

Diagrams A-H

polated and do not disturb the fundamental A-V nodal rhythm. This makes it clear that the ventricular rate will be doubled (Fig. 9), but this tachycardia, so shown, does not represent a continuous reciprocal rhythm. The first beat of the couple shows the inverted retrograde P wave within the ST or T complex and, even if the P wave is hidden in the T wave, there is some slight difference between the final deflection of the A-V nodal beat and the reciprocal beat (Fig. 9).

Interpolated reciprocal beats have never been reported in man, but Scherf was able to produce interpolated "return extrasystoles" in the experimental

I Reciprocal beats causing slowing in forward conduction. Constantly remaining retrograde conduction.



J Variation in R-P intervals due to variation in antegrade conduction. Conduction-disturbance in the course of the reciprocal pathway resulting in delayed A-V nodal discharge. The delayed nodal discharge shifts the A-V nodal rhythm and is responsible for the prolonged P-P interval following two normal P-P intervals.

K Reciprocal beat in sinus rhythm. Functional dissociation and continuous reciprocal rhythm leading to tachycardia.

L The continuous reciprocal rhythm is not initiated by a sinus beat but by a premature ventricular contraction.

M Reciprocal beats in sinus bradycardia. Auricular and ventricular bigeminy in the first and last group. Between those groups auricular bigeminy.

A series of diagrams illustrating the mechanism involved in various types of reciprocal rhythm.

Conventions are those used customarily. The direction of the arrows indicates the direction of the spread of the stimulus.

Diagrams I-M

animal. According to this author, the stimulus is conducted downward by another pathway or else it does not break into the A-V node because it is "protectively blocked."

In the second part of Diagram B, a tachycardia composed of groups of couplets is shown in which both beats have exactly the same appearance. The first beat of the couplet is an A-V nodal beat; the premature beat is a reciprocal beat, in spite of the absence of any P-wave inversion. This pattern was seen in Fig. 9. The reversal of the stimulus took place above the A-V nodal pacemaker without

exciting the auricle. Occasional aberration imitating ectopic ventricular beats was seen in the first reciprocal beats but never in the first beats of the bigeminal groups.

The absence of P waves in this pattern proves the correctness of the assumption of Langendorf, Katz, and Simon[8] that the "sandwiching" of the inverted P wave merely indicates retrograde conduction and is not an essential part in the mechanism of the reciprocal rhythm.

Diagram C illustrates an A-V nodal rhythm with progressively increasing retrograde conduction. The short P-R interval changes gradually to an R-P interval. When the inverted P wave falls sufficiently late enough, i.e., clear off the refractory period of the preceding ventricular beat, then reentry, affecting ventricular response, can take place (Drury,[17] Blumgart and Gargill,[18] and Katz and Kaplan[19]).

Diagram D shows the start of the same pattern, namely, A-V nodal rhythm with gradually increasing retrograde conduction. In the third beat, one would expect an inverted P wave falling in late enough to give rise to a reciprocal response. Instead, there is a dropped auricular beat. This is, in some way, a manifestation of the Wenckebach phenomenon (Drury[17] and Katz and Kaplan[19]).

Diagram E displays Scherf's return extrasystole which this author produced in his experimental studies on dogs.[3,4,20] After the production of a series of ventricular extrasystoles, the last one returned and again reached the ventricle. In numerous experiments, Scherf was able to produce very interesting phenomena, such as couplets and triplets, interpolated reciprocal beats, and alternation of the R-P interval. A similar condition occurs in human beings following idioventricular beats or premature ventricular beats (Levin,[23] Samojloff and Tschernoff,[5] Malinow and Langendorf,[9] Langendorf, Katz and Simon,[8] and our Case 1).

Diagram F shows a case of ventricular paroxysmal tachycardia with retrograde conduction, reciprocal beat, and retrograde block, exhibiting the Wenckebach phenomenon. This case was described by Malinow and Langendorf.[9] The first three beats are idioventricular beats with retrograde conduction. The third beat shows prolonged retrograde conduction to the auricle and is followed by a reciprocal beat. This last beat has a normal QRS complex, whereas all the other ventricular complexes show the wide QRS of idioventricular beats.

Diagram G illustrates the pattern seen in our Case 2. There is an A-V nodal rhythm with first-degree A-V block, associated with auricular and ventricular bigeminy. There are four conductions within one bigeminal group. Two impulses travel up to excite the auricle and two impulses pass down to the ventricles. The stimulus goes through the bundle three times in a relatively short time. Within one couplet, there are two inverted P waves. The first one is due to simple retrograde conduction from the A-V node; the second one represents a reciprocal auricular beat. The time of the last nodal discharge within one group can be determined in Figs. 4 and 5 by the difference between an A-V nodal interval which contains a reciprocal beat and the normal A-V nodal interval. For the sake of simplicity, the point which represents the second nodal discharge has been drawn under the assumption that retrograde conduction from the

A-V node to the auricle is the same as in the primary nodal beat. However, there is no proof at which time this point was reached or even whether the nodal pacemaker has been discharged at all. If one could prove that the nodal pacemaker was not discharged by the retrograde course of the reciprocal impulse, the theory of longitudinal functional dissociation of Scherf would be greatly supported.

Decherd and Ruskin[6] found repeatedly in their Case 3 two inverted P waves within one couplet. The first P wave was caused by rapid retrograde conduction; the second P wave, arising apparently from the same focus, had a long R-P. According to these authors, those instances proved the existence of a double auricular pathway from the A-V node. An alternative explanation should be considered; namely, that the second P wave is reciprocal to the preceding beat (similar to the pattern shown in Diagram G). Another case with two inverted P waves, but without reciprocal ventricular response, was reported by Danielopolu and Proca.[39]

The fourth group in Diagram G shows an auricular bigeminy. There is no response of the ventricle. A similar condition in an A-V nodal rhythm with reciprocal beats is illustrated in Diagram H and was reported by Langendorf.[10] The fifth A-V nodal beat shows an inverted retrograde P wave which is not conducted to the ventricle. In spite of the failure of the ventricular response, the next ventricular beat occurs at the same time as in the previous groups which contain a reciprocal beat and not after the rhythmic interventricular interval. The nodal pacemaker has been discharged by the blocked reciprocal beat without affecting a ventricular contraction. This is a good illustration of "concealed" A-V conduction and its effect on subsequent impulses.[10]

Diagram I illustrates a pattern encountered in our Case 3. It shows reciprocal beats and also a slowing in antegrade conduction caused by the preceding beats. Two consecutive P-P intervals are identical in length, but the following P-P interval is shorter since it does not contain a reciprocal beat. The constancy of those P-P intervals in the presence of gradually decreasing R-P intervals indicates slowing in antegrade conduction, whereas the time of retrograde conduction remains the same. There is an A-V nodal rhythm with constant retrograde conduction but progressively increasing forward conduction, which is caused by the reciprocal beat. After the second reciprocal beat, forward conduction is so delayed that QRS and P fall together, causing a dropping of the next expected reciprocal beat. This "dropped" reciprocal beat has a similar effect on the following complex as a dropped beat during the Wenckebach phenomenon.

Diagram J again shows that retrograde conduction remains constant whereas antegrade conduction varies. In the second bigeminy of each group, a delay in the course of the reciprocal conduction can be seen leading to a late discharge of the A-V node. The result is that the following P-P interval becomes longer than the two preceding P-P intervals. The complex following the delayed nodal discharge shows again discharge of the nodal pacemaker by a blocked reciprocal stimulus. This pattern was seen in Fig. 8.

Diagram K represents the mechanism of conduction seen in Case 1. It shows reciprocal beats occurring in sinus rhythm, functional dissociation, and tachycardia caused by continuous reciprocal rhythm.

Diagram L shows almost the same picture, but here the continuous reciprocal rhythm is not initiated by the sinus beat but by the second beat which represents a ventricular extrasystole with retrograde conduction (Fig. 2). A similar condition was reported by Samojloff and Tschernoff.[5]

The last diagram, M, illustrates reciprocal beats occurring during sinus bradycardia. The first and last couplets show auricular and ventricular bigeminy. Between these couplets are groups of auricular bigeminy which are due to blocked premature beats. The distance between the sinus beats is always the same whether the reciprocal auricular beats are followed by ventricular response or not. The possibility exists, but cannot be proved, that the longer R-R intervals contain a blocked reciprocal beat which discharges the A-V node without affecting ventricular response. The same phenomenon could be proved during the A-V nodal rhythm (Diagrams G, H, and J) since the discharge of the A-V node shifted the A-V nodal rhythm. Here, however, the possible discharge of the A-V node does not shift the sinus rhythm.

In the foregoing discussion, various types of reciprocal conduction have been explained. It is clear, however, that our diagrams do not represent all possible patterns and that many other varieties of reciprocal rhythm in combination with other rhythms are possible. The literature has always emphasized that reciprocal rhythm occurs almost exclusively in A-V nodal rhythm. Therefore, it seems to be of some importance to stress that this phenomenon may also occur in sinus rhythm. The cases of Wolferth and McMillan,[24] Naim,[7] and recently of Codina-Altés and Pijoan de Beristain[11] have shown this. Our Cases 1 and 2 are herein presented as further proof of this occurrence.

Among the thirty-four cases encountered in the literature, including our four cases, organic heart disease was found to be present in twenty-one. In three patients, only slight cardiac enlargement without any other evidence of organic heart disease was reported. Two patients gave a history of diphtheria and one patient a history of typhus. In the remaining group, this phenomenon of reciprocal rhythm was found in various conditions without any cardiac involvement or, also, in otherwise healthy people.

It is of interest to note that the case of Cutts,[16] our two reported cases, and the questionable case of Miller[31] occurred in congenital heart disease and, moreover, that this condition was observed as a transitory event in two additional patients during a Blalock-Taussig operation.

SUMMARY

Three cases which exhibit the rare phenomenon of reciprocal rhythm are analyzed and described in detail.

Extraordinarily rare and partially unknown features were encountered. These consisted of tachycardia due to continuous reciprocal rhythm, of tachycardia caused by interpolated reciprocal beats with and without eliciting auricular

contraction, of the occurrence of reciprocal rhythm in sinus rhythm and in A-V nodal rhythm with first-degree A-V block, of discharge of the nodal pacemaker by blocked reciprocal beats, and of allorhythmia due to the effect of reciprocal beats on sequential beats.

In addition, a hitherto unreported disturbance of conduction is described; namely, the occurrence of a disturbance in the course of the reciprocal pathway which results in late discharge of the A-V nodal pacemaker.

A short tracing of another patient, taken during a Blalock-Taussig operation, is shown which demonstrates pseudoreciprocal and reciprocal rhythm.

The literature is reviewed, and diagrams illustrating the mechanism involved in various types of reciprocal beating, as encountered both in the literature and in our own cases, are shown and discussed in detail.

ADDENDUM

Since this article was submitted, Pick and Langendorf's paper (Pick, A., and Langendorf, R.: A Case of Reciprocal Beating With Evidence of Repetitive and Blocked Re-Entry of the Cardiac Impulse, Am. Heart J. **40**:13, 1950) has appeared. Their case was strikingly similar to our Case 3 and showed also the disturbance of conduction, previously described, which we explained on the assumption of a delay in the course of the reciprocal pathway and which, to our knowledge, had not been hithertofore described. Pick and Langendorf's assumption of a repetitive re-entry mechanism, which could be proved in their case, seems to us a very interesting and absolutely possible alternative explanation for our case.

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Clinical Reports

ACUTE ARTERIAL THROMBOSES INVOLVING MAJOR VESSELS

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THIS is a report of a patient who developed widespread acute multiple thromboses, involving the major arteries of the brain, abdomen, and upper and lower extremities.

CASE REPORT

S. J., a 57-year-old white woman, was admitted to the hospital on Oct. 4, 1946, with the complaints of ankle edema, frequency of urination, some exertional dyspnea, anorexia, nausea, and vomiting occurring intermittently for one year. There was a sixteen-year history of diabetes mellitus, necessitating of late the use of 25 units of regular insulin daily. Hypertension was present for many years.

Physical Examination.—The heart was enlarged to the left; no murmurs were heard; the blood pressure was 210 mm. Hg systolic and 110 mm. Hg diastolic. The chest was flat to percussion at both bases. The liver was enlarged, its edge about five fingerbreadths below the right costal margin. Ankle edema was pronounced. Diabetic retinopathy was present.

Laboratory Data.—The urine showed 3 plus albumin, 3 plus glucose, and no acetone. In the peripheral blood there were 13,700 white blood cells per cubic millimeter with a normal differential count; the sedimentation rate was 25 mm. per hour, and the coagulation time was two minutes by the Lee-White method (the normal varies from five to ten minutes). The blood glucose was 290 mg. per cent; the nonprotein nitrogen was 43 mg. per cent; the serum albumin was 1.6 Gm. per cent, the globulin 2.8 Gm. per cent with an A/G ratio of 0.62. The cholesterol was 342 mg. per cent and the esters 217 mg. per cent. The venous pressure was 58 mm. of water. A roentgenogram of the chest showed marked cardiac enlargement with fluid at both bases.

The electrocardiogram showed a regular sinus rhythm, a depressed RST complex in Leads I and II, with T_1 inverted and a low-voltage T_3.

Course.—The patient received mercurial diuretics by injection, ammonium chloride, and a low salt diet. In three days the peripheral edema was much diminished. On the morning of the eighth hospital day, no arterial pulsations were found in the left arm below the brachial fossa. Marked pallor and paresis of the hand were noted. The blood pressure could not be determined. Papaverine hydrochloride was given by vein. A left stellate ganglion block was done, but only transient relief was obtained. Ice packs were applied to the forearm. Because of the absence of pulse and blood pressure, the cold, clammy, cyanotic appearance of the forearm, and the poor response to intravenous papaverine, ice packs, and stellate ganglion infiltration, the patient was operated upon during the evening of the eighth hospital day. A thrombus was removed from the mid-portion of the left brachial artery. Stellate ganglion infiltration was repeated after the operation. Upon return from the operating room, the patient received heparin by slow intra-

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venous drip. However, there was little change in the clinical condition. Later that same evening, the patient suddenly became comatose with almost complete absence of reflexes. She responded well to intramuscular Coramine and caffeine. On the ninth hospital day, another stellate ganglion infiltration was done with equivocal results. There was no change in the condition of the left forearm. In order to diminish reflex vasospasm, an arteriectomy was performed; 28 mm. of the left brachial artery were resected. Heparin infusion was stopped and Dicumarol substituted. On the tenth hospital day, a fourth stellate block was done with infiltration of the second, third, and fourth sympathetic ganglia. During the day the patient complained of severe pain and coldness in the left lower extremity. Cyanosis was noted with the absence of arterial pulsations. No readings were obtained with the oscillometer. A left lumbar sympathetic block with procaine was done with slight amelioration of the patient's symptoms. This was repeated later that day and the following day. Because of a relatively normal coagulation time on this day (four minutes), in spite of a prothrombin time of ninety-five seconds, heparin therapy was started again with a dose of 100 mg. every four hours. The coagulation time now ranged from eleven minutes to forty-five minutes. On the eleventh hospital day, the pulse in the right upper extremity could not be felt, and the blood pressure could not be measured. The patient's condition deteriorated progressively, as she failed to respond to medication. She expired on the thirteenth hospital day. An autopsy was performed on the same day, seven hours post mortem.

Necropsy Report.—The body was that of a white woman, 139 cm. long, with some cadaveric rigidity. The skin of the left forearm and hand was moderately blue-violet and slightly edematous; the skin of the fingers was wrinkled and purple. The sutured operative wound was visible on the left upper extremity.

The inferior edge of the liver was 4 cm. below the right costal margin. The right pleural cavity contained 400 c.c. of turbid yellow fluid, and the left contained 200 c.c. The pericardial sac was normal.

The heart weighed 360 grams. Numerous calcified atheromatous plaques were seen in the sinuses of Valsalva. Several coarse atheromatous plaques were noted in the pulmonary artery and the ascending aorta. There were no thrombi in the auricles. The left ventricular myocardium was mottled with indistinct yellow-green and purple areas, most marked over the interventricular septum. The posterior papillary muscle was flat, purple, and on section alternating purple and yellow-gray areas were present. The coronary arteries were sclerotic, narrowed, and tortuous. No occlusions were found. Two flat subintimal hemorrhages, about 3 to 4 mm. each, were visible in the right coronary artery without an overlying thrombus. Most of the aorta was inelastic, and the lowermost portion of the abdominal aorta was converted into a rigid tube. Calcified plaques were numerous. Several subintimal hemorrhages were seen.

The lungs were atelectatic. The neck organs, including the four parathyroids, were normal. The kidney surfaces were smooth with an occasional scar. On section, moderate reduction in width of the cortex was noted. The arteries gaped on cross section, and intimal plaques were visible. There were no macroscopic thrombi. The right renal artery arose from the aorta 2 cm. above the celiac axis. The spleen, adrenals, and the urinary bladder showed no abnormality. The esophagus, stomach, and duodenum were normal.

The liver weighed 1290 grams; its cut surface was yellow-brown. The gall bladder was normal. The pancreas showed chalky yellow spots in places and was fatty throughout. Samples of the sternum, ribs, and vertebrae were porotic.

The left common carotid, internal and external carotids, lingual, subclavian, and axillary arteries were patent. At 19.5 cm. from the aorta, a black suture was tied about the left brachial artery. There was a fresh thrombus extending 1.7 cm. proximal to the suture. Three cm. of the artery distal to the suture were absent (removed at operation). Another black suture was tied about the proximal end of the distal segment of the vessel. Distal to this ligature for a distance of 3 cm., the artery was occluded by a fresh thrombus. Beyond this point, for 3 cm. the occlusion was composed of partly organized thrombus over atheromatous plaques. Beyond, the artery became patent. The profunda brachii contained a fresh occluding thrombus 1.5 cm. long. The right brachial artery at 16 cm. from the aorta was occluded by a fresh thrombus for a distance of 2 cm. It was then segmentally occluded to its bifurcation. The right radial and ulnar arteries were occluded at their origin; beyond, their lumina were free again. The right profunda brachii, subclavian, axillary, and internal and external carotid arteries were patent.

Three cm. from its origin, the splenic artery was occluded for a distance of 3 cm. by an old thrombus. The vessel was very tortuous and sclerotic. The gastroduodenal and pancreaticoduodenal arteries were occluded by firm gray thrombi. The left gastric artery was patent. The mouth of the superior mesenteric artery was firmly occluded by a projecting, irregular, red-gray thrombus. The lumen was 0.6 cm. wide, 1.6 cm. distal to its origin. The occlusion then became complete for 2.5 cm. The next 3 cm. were partially occluded, after which the lumen became patent. The first centimeter of the left colic artery was occluded by a recent thrombus. The common, external, and internal iliac arteries were patent.

Thirteen cm. from the aortic bifurcation, the left femoral artery was occluded for 1 cm. by a fresh thrombus. Distal to this point, it was partially occluded for 2 cm., after which the lumen was reduced to a narrow slit. The left profunda femoris was totally occluded by a fresh thrombus over atheromatous plaques as far as Hunter's canal. The right femoral artery, at a distance of 18 cm. from the aortic bifurcation, was partially occluded for 0.5 cm. by a fresh thrombus. For 3 cm. beyond, the occlusion was made complete by a pale gray thrombus with atherosclerotic masses. The following 3 cm. were occluded by a homogeneous fresh thrombus. The right profunda femoris was patent, but many of its branches were occluded.

Brain.—The pituitary and pineal glands were grossly normal. There was softening of the right cerebellar lobe. The left vertebral artery was occluded for a distance of 2.5 cm. by a fresh thrombus. The rest of the vessel was occluded by atheromatous masses. The first 2 cm. of the basilar artery were patent. Beyond that point, a fresh occluding thrombus was noted, extending to the division into right and left cerebral arteries. The right cerebral artery was occluded by a fresh thrombus for 2 cm., and the left cerebral artery was occluded for 1 cm. The left posterior cerebellar artery was occluded for a distance of 1 cm. by a fresh thrombus.

Microscopic examination.—Several areas of necrosis were seen in the anterior papillary muscle. The posterior papillary muscle showed necrosis, vacuolization of muscle fibers, and small collections of round cells. A similar picture was seen in the sections from the interventricular septum. The left anterior descending coronary artery showed extreme sclerosis with narrowed lumen, thinned media, and some calcification. The lungs showed a good deal of variation in the width of the alveolar spaces, some of which were collapsed. Arteriolosclerosis of the blood vessels in the adrenal glands was marked. Extensive thickening of the glomerular tufts was noted in the kidneys. Little fat was seen in the liver, but marked central stasis was noted. There was marked atrophy of the pancreas with moderate fibrosis. Some hyaline areas were seen in the islands of Langerhans. No blood vessel lesions were noted in the sections from striated muscle.

There was hemorrhage in one of the large atheromatous lesions in the aorta. The lumen of the basilar artery contained a fresh thrombus. Intimal hyperplasia was marked with splitting of the elastic lamina and calcification in places. The temporal artery was the seat of cellular intimal thickening. The right brachial artery contained a fresh thrombus in its lumen. There was pronounced intimal hyperplasia and widespread leucocytic infiltration in the media and adventitia accompanied by destruction of muscle. In other sections at other levels, atherosclerosis was marked, but the media was intact. In the left brachial artery no inflammation was seen in the sections of the proximal portion. Leucocytes and fibrin were found in the outer layers in the distal portion. Otherwise the picture was the same as the right brachial artery. The right femoral artery showed a complete fresh occlusion with calcification. In the left femoral artery, there was fresh thrombosis and severe atherosclerosis. Portions of the media were infiltrated with round cells. The lumen of the splenic artery was almost obliterated, the occluding mass consisting entirely of collagen and elastic lamellas. In the pancreaticoduodenal artery beginning organization of the thrombus was noted with intimal hyperplasia filling half of the lumen. The outer portion of the media and adventitia was densely infiltrated with leucocytes and plasma cells. The superior mesenteric artery showed much the same picture except for much less inflammation.

Anatomical diagnosis.—Severe generalized atherosclerosis. Fresh thrombosis of the right and left brachial, left profunda brachii, right radial and ulnar, superior mesenteric, left colic, right and left femoral, left profunda femoris, left vertebral, basilar, right and left posterior cerebral, and left posterior superior cerebellar arteries. Organized thrombosis of the right and left femoral, splenic, pancreaticoduodenal, gastroduodenal, and superior mesenteric arteries. Subintimal hemorrhages in the right coronary artery and aorta. Severe nephrosclerosis. Origin of the right renal artery above the celiac axis. Myocardial necrosis.

DISCUSSION

Acute arterial thrombotic occlusion in one or several arteries has been reported.[1-7] In most of these cases the post-mortem studies were inadequate, since the arterial tree was not completely removed. While it is customary to think of widespread occlusive vascular disease as being peculiar to the older age group, extensive vascular occlusions have been demonstrated in patients from the age of 2 days to 30 years.[8-11]

This case is reported for several reasons. As can be seen from the post-mortem protocol, most of the arterial tree was dissected, leaving little doubt as to the extent of the thromboses. The absence of thrombi in the heart removed embolization as an explanation for the pathogenesis. No thrombi were found in the femoral veins. The rapidity with which the acute arterial thromboses developed, as well as their diverse locations, presented an extremely unusual problem. Arterial thromboses in the upper extremities are an infrequent finding.[12-14] Of equal interest were the older asymptomatic occlusions of the major abdominal arteries. Undoubtedly, an extensive collateral system had been developed.

Fatheree and Hines[15] in studying cases of thromboangiitis obliterans in the extremities found widespread arterial disease affecting the viscera and brain in which typical inflammatory lesions were not found. In our case, careful study of many microscopic sections from the vessels of all extremities did not show any characteristic lesion of the latter disease. The absence of generalized severe medial and adventitial inflammation with thrombus organization, and the presence of severe extensive atherosclerosis with occasional calcification make the diagnosis of thromboangiitis obliterans improbable in our case. The occasional medial inflammation, most marked in the right brachial artery, was believed to be secondary to the acute thrombosis. The diagnosis of periarteritis nodosa was discarded because of the absence of necrosis and aneurysm formation. The extensive arterial disease takes this case out of the group of essential thrombophalia.[16] No evidence of trauma was found. The role of intimal hemorrhage in the genesis of arterial thrombosis was considered,[17] but study of the microscopic sections did not support such an hypothesis in this case. Serial sections of these lesions might add much valuable information. Patterson[17] has frequently emphasized that the origin of arterial thrombi can be traced to minute subintimal hemorrhages which are often overlooked. In retrospect, we question the role of heparin and Dicumarol in initiating further hemorrhage and subsequent thrombus formation. The evidence is insufficient to answer this question.

Arteriosclerosis was widespread and severe with intimal hyperplasia occluding some of the vessels. Diabetes mellitus had been present for sixteen years. The use of intensive dehydration therapy may have produced some derangement in the clotting mechanism. The presence of some thrombosing tendency was indicated by the initial clotting time of two minutes (Lee-White). Whether or not physical factors were involved in producing a slowing of the blood stream with eddy formation, because of marked segmental narrowing of the arterial lumen, cannot be stated with certainty. There has been little study of the dynamics of circulation in relation to thrombus formation. The role of protamine

as an antiheparin is now receiving increased attention; many patients, however, have received protamine zinc insulin for long periods of time. The role of protamine in enhancing thrombosis in diabetics is entirely conjectural.

We think that the combination of diabetes mellitus, severe atherosclerosis, rapid dehydration, and increased blood coagulability were the main factors in precipitating the extensive vascular occlusions in this patient. The older thrombi indicated perhaps that only the tempo of the process had been accelerated. The exact mechanism underlying this sudden generalized arterial thrombosis is still unknown. However, such cases do occur.[12] According to Leriche and Stecker,[18] extensive thrombosis may occur suddenly in an atherosclerotic vessel. Diabetics may show no evidence of occlusion for years; suddenly, signs of vascular thrombosis will develop. Our case falls into this group.

SUMMARY

The case of a 57-year-old woman with acute multiple arterial thromboses involving the entire arterial tree is presented. The etiological factors were obscure.

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MULTIPLE PULMONARY EMBOLI FROM RIGHT AURICULAR THROMBI

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THE realization of the importance of the problem of thromboembolism in the past decade has led to a great deal of study in an effort to determine the common sites of thrombosis from which pulmonary and systemic emboli arise. Most systemic emboli arise, of course, from the left side of the heart. There are those[1,2a] who once felt that the vast majority, perhaps 95 per cent, of pulmonary emboli arise from thromboses in the lower extremities. Little attention was paid to the heart as a source of pulmonary emboli.[2b] This latter view has been challenged recently by Van der Veer and associates[4] and by Zahn and Peirce.[3] The frequency of mural cardiac thrombi and their importance as a source of multiple pulmonary and systemic emboli is now being clearly recognized.[5-17,23,24]

There are many examples in the literature of pulmonary emboli arising from right auricular mural thrombi in patients with mitral stenosis and/or auricular fibrillation, and from right ventricular mural thrombi in patients with myocardial infarction. We have been unable to find reports dealing with multiple pulmonary emboli arising from right auricular thrombi in the presence of prolonged congestive heart failure, but in the absence of mitral stenosis and/or auricular fibrillation, and without myocardial infarction. We are therefore reporting two such cases.

CASE REPORTS

CASE 1.—F. B. was a 31-year-old white man admitted with a history of recurrent, fleeting polyarthritis, epistaxis, lower abdominal pain, weakness, hemoptysis, anorexia with a 20 pound weight loss, and chilly sensations with a low-grade febrile course up to 101° F. Pallor, progressive exertional dyspnea, orthopnea, and edema had also been noted. Physical examination revealed the following pertinent features:

1. The patient was an acutely and chronically ill, 31-year-old, white man, dyspneic at rest, and orthopneic, with a very sallow complexion.
2. There was an absence of petechiae in the fundi, mucous membranes, skin, and nailbeds.
3. There were no signs of pulmonary congestion.
4. The heart was enlarged to percussion. The apex beat was in the left fifth intercostal space well outside the mid-clavicular line. A loud, long, high-pitched diastolic blow, as well as a basal systolic murmur, was noted at Erb's point. No rumbling apical diastolic murmur

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was heard. The blood pressure was 130/40 to 0 mm. Hg. Marked capillary pulsation was noted in the nailbeds, as was a pistol shot sound over the femoral arteries. Regular sinus tachycardia was present.

5. Hepatosplenomegaly was absent.
6. Pallor of the nailbeds and clubbing of the terminal phalanges were noted.
7. The neck veins appeared normal; no peripheral edema was noted.

Fluoroscopy revealed marked left ventricular enlargement, moderate left auricular enlargement, and marked aortic pulsations. The right side of the heart was dilated. Venous pressure measured 160 mm. of citrate with a rise to 200 mm. on right upper quadrant pressure. The Decholin arm-to-tongue circulation time was 21 seconds.

The admission diagnosis was: rheumatic heart disease with superimposed, subacute bacterial endocarditis and possible active carditis.

The electrocardiogram showed a pattern of left ventricular hypertrophy with a vertical position of the heart electrically. Regular sinus rhythm was present. The admission hemoglobin was 8.6 Gm., red blood cell count 3.2 million, white blood cell count 10,400, with a normal differential. Urinalysis and serology were normal. Despite repeatedly negative blood cultures, the diagnosis of subacute bacterial endocarditis was made, and the patient was treated with 4.5 million units of penicillin daily. Further treatment consisted of digitalization, mercurials, a salt-free diet, and transfusions. The patient's condition improved at first, but then bouts of severe dyspnea, cyanosis, and free perspiration developed. The etiology of these bouts was initially obscure. However, when hemoptysis also developed, it was felt that the patient was having multiple pulmonary emboli. No evidence of thrombosis was ever found in the lower extremities. The diagnosis of right-sided subacute bacterial endocarditis was entertained in view of the negative blood cultures and repeated bouts of pulmonary infarction, which were, however, not septic. X-ray confirmation of these pulmonary infarcts also developed. Despite intensive chemotherapy, which included penicillin and later streptomycin, the patient went downhill gradually. The clinical picture was dominated by the repeated bouts of pulmonary emboli with fever, hemoptysis, and cough.

At post-mortem examination multiple pulmonary emboli with areas of pulmonary infarction were found. The heart weighted 550 grams. The coronary arteries were normal. All the valves were normal except for the aortic valve which was insufficient and contained a large ulcerating vegetation on all three cusps. Gram-positive cocci were found on smear. A culture was taken from this vegetation, but unfortunately it was found to be of little value because of contamination. All chambers of the heart were dilated. Small collections of lymphocytes and mononuclear cells were noted, interspersed between the ventricular muscle bundles around dilated capillaries. No true Aschoff bodies were found. A large premortem friable thrombus was found, filling the entire right atrial appendage. The auricular wall beneath the thrombus was infiltrated with polymorphonuclear cells. The myocardium of the right atrial appendage itself appeared necrotic. No evidence of venous thrombosis was found elsewhere in the body. Old splenic and renal infarcts were found.

The final pathological diagnoses were: (1) rheumatic heart disease, inactive; subacute bacterial endocarditis on the aortic valve; enlarged heart, aortic insufficiency, aortic valve; bacterial endocarditis, right atrial appendicular thrombus; and (2) multiple pulmonary emboli and infarcts.

CASE 2.—H. M. was a 44-year-old white man admitted with a history of migratory polyarthritis at the age of 19 years. A heart murmur was heard for the first time when the patient was 28 years old. Three months before admission, the patient noted the onset of exertional dyspnea, two-pillow orthopnea, and paroxysmal nocturnal dyspnea. Despite digitalization, his symptoms continued, and he was therefore hospitalized. Physical examination revealed the following features:

1. The patient was a chronically and acutely ill, 44-year-old, white man with a sallow complexion.
2. The neck veins were dilated and filled from below.
3. Moist inspiratory râles were heard at both lung bases.
4. The heart was enlarged to percussion. The apex beat was in the fifth left intercostal space well outside the mid-clavicular line. A harsh, systolic aortic murmur transmitted to the neck was heard. A long, loud diastolic blow was present at Erb's point. No rumbling apical

diastolic murmur was heard. There was no thrill at the base, and the second sound at the aortic area was normal. Blood pressure was 104/60 mm. Hg. Regular sinus tachycardia was present.

5. The liver was felt 2 fingerbreadths below the costal margin. Splenomegaly was absent.
6. The nailbeds were pale, but clubbing was absent.

Fluoroscopy revealed marked left ventricular enlargement, a prominent pulmonary artery with bilateral pulmonary congestion, moderate enlargement of the left auricle, right auricle, and right ventricle, and a relatively inconspicuous aortic knob. The venous pressure was 200 mm. of citrate with a rise to 240 mm. on right upper quadrant pressure. The Decholin circulation time was 40 seconds.

The admission diagnosis was: rheumatic heart disease (inactive); enlarged heart, aortic insufficiency, probable aortic stenosis; possible subacute bacterial endocarditis; and congestive heart failure.

The electrocardiogram showed the pattern of left ventricular hypertrophy in an electrically horizontal heart. Regular sinus tachycardia was present. Urinalysis was normal. The white blood cell count and differential were normal. Hemoglobin was 13.2 Gm. and the red blood cell count was 4 million. On bed rest, digoxin, mercurials, and a salt-free diet, the patient showed a good therapeutic response at first. As in the first case, bouts of dyspnea, cyanosis, perspiration, and hemoptysis together with areas of pulmonary infarction appeared on the roentgenogram. Repeated blood cultures were negative. A course of penicillin was given without effect. The patient went downhill and died some four weeks after admission.

At post-mortem examination multiple pulmonary emboli and infarctions were found in both lungs. No peripheral vein thromboses were found. On the contrary, a friable polypoid thrombus was found attached to the wall of the right auricular appendage. The underlying auricular wall was normal. The heart weighed 850 grams. All chambers were dilated, with predominant left ventricular hypertrophy. The coronary vessels were normal. All valves were normal except for the aortic valve. The latter valve was rigid and calcified and showed marked stenosis. A large, warty, calcified vegetation was noted on all three cusps, extending down into the sinus of Valsalva. Partial fusion of the cusps was present. The vegetation was completely calcified with no fresh friable components. No stigmas of healed rheumatic carditis were noted. Several old renal infarcts were present.

The final pathological diagnoses were: (1) healed subacute bacterial endocarditis; possible inactive rheumatic heart disease; enlarged heart, aortic insufficiency, and aortic stenosis; and (2) multiple pulmonary emboli and infarcts.

DISCUSSION

In view of the recent reports[18-21] of the beneficial therapeutic effect of anticoagulant therapy in congestive heart failure, we must explain why such therapy was not pushed in these two patients in an attempt to halt the pulmonary embolization. Actually, Dicumarol was employed for a few days in the first patient, but it was discontinued when rectal bleeding developed. Anticoagulant therapy was not given to the second patient because of the possibility that subacute bacterial endocarditis complicated the situation. The danger of hemorrhage, especially cerebral hemorrhage, in patients with subacute bacterial endocarditis who are given Dicumarol or heparin made us decide against exploitation of such therapy.[25]

The etiology of auricular thrombi has been elucidated in several papers.[6,12,22] Graef and co-workers[22] studied 178 cases of rheumatic heart disease and found auricular thrombi in twenty-four patients. There were fourteen examples of left auricular thrombi, five examples of right auricular thrombi, and five examples of bilateral auricular thrombi. In all ten patients with right auricular thrombi, the thrombus was confined to the right auricular appendage. Mitral

stenosis was present in all ten. Furthermore, five of these ten patients had an irregular rhythm, namely auricular fibrillation. It can thus be seen that no case similar to the two described in this paper was noted by Graef and co-workers.

Garvin[6] studied the incidence of mural cardiac thrombi in 771 autopsied patients. There were 116 instances of rheumatic heart disease in this series. Garvin felt that the presence of auricular fibrillation bore a highly significant relationship to the occurrence of auricular thrombi in patients with rheumatic heart disease, having noted that 43 per cent of sixty patients with auricular fibrillation had auricular thrombi, while only 18 per cent of fifty patients with sinus rhythm had auricular thrombi. This relationship was not found in other types of heart disease.

Söderström[12] has made the most detailed study of atrial thrombosis yet published. He noted that it was possible to distinguish two types of mural thrombi in the left atrium. "Surface thrombi" developed in the smooth part of the left atrium, probably caused by a mural endocarditis. "Recess thrombi" were noted in the left auricular appendage, without relation to an underlying atrial wall lesion, but probably secondary to stagnation of blood in prolonged congestive heart failure or auricular fibrillation. Right atrial thrombi were noted to be uniformly of one type and confined to the right auricular appendage. Atrial wall lesions, usually with more or less extensive myocardial infarcts involving the auricular musculature, were found beneath most right atrial thrombi. Söderström found that patients with left atrial thrombi showed a higher incidence of auricular fibrillation than other groups of patients dying of heart disease. However, no significant correlation could be demonstrated between right atrial thrombi and auricular fibrillation. This author partly attributed right appendicular thrombi to underlying damage of the atrial wall, usually by infarction. However, the fact that atrial mural thrombi were used as indicators to find atrial wall infarctions in this series must be kept in mind, as this fact considerably alters the significance of the author's conclusions. Söderström also attributes right atrial thrombi to stagnation of blood in the atrial appendage, such as might occur in prolonged congestive heart failure.

Our two patients illustrate examples of right atrial appendicular thrombi, one due to congestive heart failure, the stagnation phenomenon, and the other due to congestive heart failure and an underlying right auricular appendage wall infarction. The etiology of the atrial wall infarct is obscure. No coronary emboli were found. The clinical picture of multiple pulmonary emboli from such lesions in the absence of mitral stenosis, auricular fibrillation, and ventricular myocardial infarction has not been previously described. Söderström mentions seven cases in which pulmonary emboli were found in the presence of right atrial appendage thrombi and atrial wall infarction, but all of these cases were complicated by auricular fibrillation, mitral stenosis, or ventricular myocardial infarction, with the latter a possible source of right ventricular thrombi.

One further point deserves comment. In the second patient the age of the healed subacute bacterial endocarditis lesion was placed at at least several months by the pathologist. In view of the fact that the patient received no chemotherapy prior to his admission, and in view of the fact that the total dura-

tion of his hospital stay before death was only one month, the conclusion that this patient represented a case of spontaneous cure of subacute bacterial endocarditis seems inevitable.

SUMMARY

Two cases with multiple pulmonary emboli and infarctions ending fatally are described. In both instances the only source noted for these emboli was a right atrial appendage thrombus found in the absence of mitral stenosis and auricular fibrillation. In neither case was a thrombus found in the right ventricle.

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Book Reviews

ADVANCES IN INTERNAL MEDICINE. William Dock and I. Snapper, Editors and Associates. Volume IV, Chicago, 1950, The Year Book Publishers, Inc., 549 pages. Price $10.

Volume IV of *Advances in Internal Medicine* contains two sections which are of particular interest, namely, "The Use of Sodium Depletion in Therapy," by William Dock and "Clinical Use of Anticoagulants" by J. Earle Estes and Edgar V. Allen. As both these subjects are still open to considerable controversy, the reviews would seem to be most timely. Therefore, it would be well if all physicians would read these chapters carefully, since the hazards as well as the virtues of these methods of treatment are thoroughly explained by the authors.

M.

THE 1950 YEAR BOOK OF MEDICINE. Paul B. Beeson, J. Burns Amberson, William B. Castle, Tinsley R. Harrison, and George B. Eusterman, Editors. Chicago, 1950, The Year Book Publishers, Inc., 819 pages. Price $5.

The 1950 Year Book of Medicine contains five parts, the most important one for the cardiologist being No. 4, "The Heart and Blood Vessels and the Kidney," written by Dr. Tinsley R. Harrison. There are here reviewed the outstanding publications. For the busy internist this provides an excellent source of reference as the reviews of the various articles are clear and concise and easily readable.

M.

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY. Eighth Edition, Rahway, N. J., 1950, Merck and Co., Inc., 1592 pages. Price $5 (Thumb index edition).

The eighth edition of *The Merck Manual of Diagnosis and Therapy* is up to the excellent standards of its predecessors. It follows the general format of previous editions while adding many up-to-date changes gleaned from the current literature. In fact, there will be found here most of the advances which have proved to be of value in diagnosis and therapy over the past decade. This is particularly so with reference to antibiotic therapy and the newer vitamin preparations. As would be expected, the more recent adrenocortical and related therapy is briefly outlined and is also referred to in various chapters where its specific effects would seem to indicate favorable results. At the same time, there is constantly sounded a word of caution as to the use of these therapeutic measures, and it is emphasized that much careful clinical study and prolonged follow-up will be necessary before the true value and optimum methods for their use can be determined.

Taking it all in all, this manual will serve a useful purpose as a source for ready reference.

M.

MANAGEMENT OF PERIPHERAL ARTERIAL DISEASES. By Saul S. Samuels, A.M., M.D. New York, 1950, Oxford University Press, 345 pages. Price $7.50.

This volume is in the way of being a monograph dealing with the author's personal experience over many years with peripheral arterial disease, special consideration being given to thromboangiitis obliterans and arteriosclerosis obliterans. Of special interest are the sections on the therapy of these and allied diseases.

This book will be of particular interest to those who do not aspire to be specialists in peripheral vascular disease as it deals with most of these lesions after a practical fashion.

M.

A MANUAL OF CARDIOLOGY. By Thomas J. Dry, M.A., M.B., Ch.B., M.S. in Medicine, Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Section on Cardiology, Mayo Clinic. Second Edition, Philadelphia and London, 1950, W. B. Saunders Company, 355 pages with 97 figures. Price $5.

The appearance of a second edition of this compact *Manual of Cardiology* is to be welcomed, in particular by the medical student and interne as well as the general practitioner. It is concise and easily readable. There is no ambiguity when the author deals with controversial matters as he has no hesitation in implying or, indeed, in stating that the matter under consideration has not as yet been definitely proved.

M.

A MANUAL OF RHEUMATIC DISEASES. By W. Paul Holbrook, M.D., and Donald F. Hill, M.D., with the assistance of Charles A. L. Stephens, Jr., M.D. Chicago, 1950, The Yearbook Publishers, Inc., 182 pages. Price $4.25.

This monograph deals briefly with the subjects implied by the title. On the first 117 pages seven types of arthritis are discussed in a simple and direct manner. Of the greatest aid to the general practitioner will be the 50 pages devoted to the prevention and correction of deformities. Until a specific cure can be found which may have universal or common acceptance without untoward hazards, these must be the aim in all patients with these diseases. For this one-third of the volume alone, it is well worthy of a place in the libraries of all medical practitioners.

M.